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Archives OF INTERNAL MEDICINE

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JUNE 1955
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Entered as Second Class Matter Jan. 23, 1909, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $10.00

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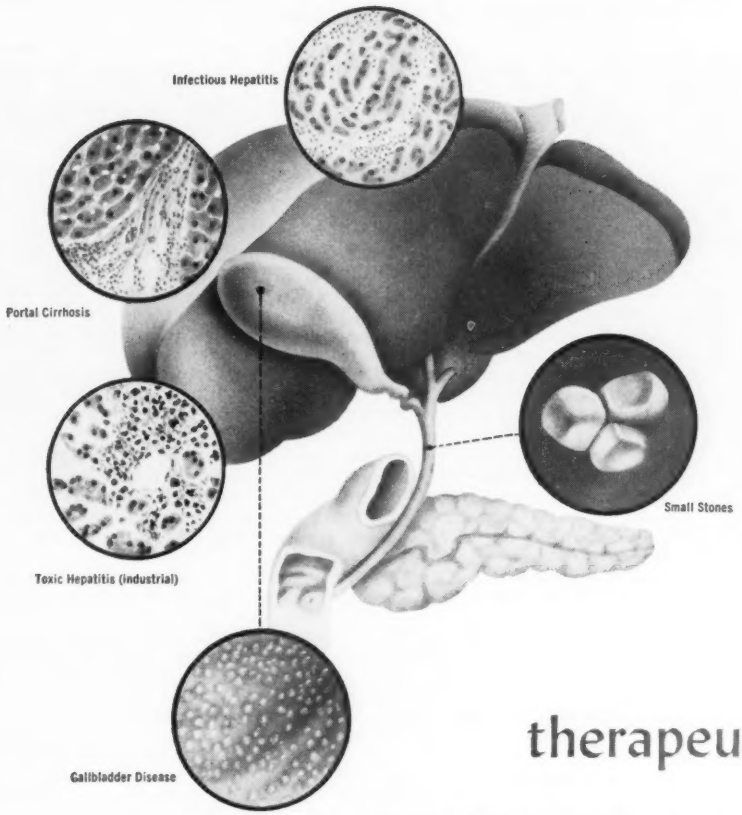

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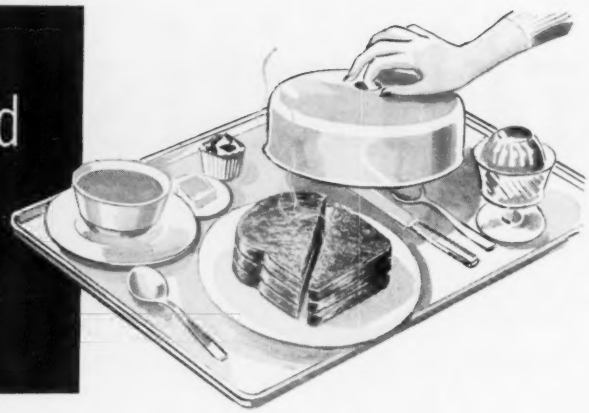

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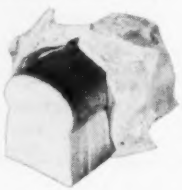

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Dyschondroplasia and Hemangiomata (Maffucci's Syndrome)

WILLIAM BENNETT BEAN, M.D., Iowa City

> If you have the good fortune to command a large clinic, remember that one of your chief duties is the tabulation and analysis of carefully recorded experience.
>
> —Osler *

Rare diseases not only have interest for the clinical connoisseur but also may bring understanding to commonplace diseases. Collectors of clinical esoterica do indeed fatten their egos by the ability to pin a proper label on a patient with an obscure disease. Nonetheless, case reports of very rare conditions are needed to accumulate information which later may be synthesized. Unusual diseases may contribute to the knowledge of genetic mechanisms, and unsuspected physical and metabolic interdependences, and mischances in the development and in the fate of embryonic tissues. Patients with rare diseases and developmental anomalies may live a long time. This adds the dimension of time, if the subject is under observation for a period long enough to delineate the natural history of growth and development. The disposition of persons with rare diseases to special accidents or complications may give additional insights into the complicating diseases. There is another compelling reason for publishing reports of rare disease. Any physician who has to care for a victim of such a devastating deformity as Maffucci's syndrome is frustrated by his inability to find the cause and correct it. Thus a final motive for publication of such case reports is the hope that if the disorder is known more widely someone may discover something to prevent or relieve the tragedy it brings to those so miserably afflicted.

Among the notable medical collectors of the unusual, Hutchinson [2] was outstanding; but in his *Archives of Surgery* there is no mention of the syndrome to which the name of Maffucci has been attached. Parkes Weber, whose clinical collecting has continued through a medical experience of more than three score and ten years, mentioned it in his delightful little book on rare diseases.[3] He did not record a personal case. The classic article on Maffucci's syndrome was written by Carleton, Elkington, Greenfield, and Robb-Smith.[4] They restored the eponymic honor of priority to Maffucci, collected all the cases published up to 1942, and lucidly discussed available knowledge of the disease. In brief, Maffucci's syndrome is an inborn dysplastic mesodermal anomaly in which dyschondroplasia and vascular hemangioma (angioma, phlebectasia, and hamartoma) occur together. My purpose is to describe three cases seen in the University Hospitals of the State University of Iowa during the last two years and to review the reports of seven additional cases reported since 1942.

Case 1.—R. H. first entered the University Hospitals, Iowa City, on June 30, 1953. She was admitted to the pediatric service for severe uncontrolled hemoptysis. She was born Jan. 1, 1940, the first of two children of normal parents with no blood relationship. Neither her sister nor any relative or forebear has had any similar trouble.

Past History.—On March 20, 1940, she was seen by a radiologist because of a large bluish angioma

From the Department of Medicine and University Hospitals of the College of Medicine, State University of Iowa.

* Quoted in Bean and Bean.[1]

on the nose, left side of the face, and ear. Her parents reported that it was fading. It was not treated. On April 22, 1940, she returned because the deep vessels of the left side and back of the neck and shoulder had enlarged. There was some difficulty with breathing. Chest films showed slight broadening of the mediastinum and compression of the trachea. From then till the middle of September several x-ray treatments were given over the mediastinum, each time with temporary improvement. Much more radiation was needed than that required to shrink an enlarged thymus, which originally was thought to be the source of trouble. Through the fall and winter superficial x-ray treatment was given over the nose, left side of the face, jaw, neck, corner of the eye, and eyebrow. By May, 1942, the angiomatous lesions were smaller, but there were large veins over the left forehead and temple. For the next five years she was seen at intervals. The vascular changes slowly became less conspicuous. In April, 1948, x-rays showed the bones of the left side of the face to be smaller than those of the right. There were no permanent teeth in the bicuspid and molar areas, except for the third molar. In August, 1949, a small papilloma on the right side of the nose was destroyed by electrocoagulation. In November, 1950, a bluish cavernous hemangioma 5 cm. wide was observed on the back, a month after an injury. In July, 1951, a hard nodule was found on the medial edge of the left scapula. X-rays revealed another, larger and denser, osteochondroma arising from the axillary side. These were removed surgically. In spite of these difficulties she had been active, grew normally, and was generally healthy until hemoptysis began, late in June, 1953, which recurred five times before her admission. X-rays taken elsewhere showed some kind of infiltrative lesion in the chest. Tuberculin and histoplasmin tests were negative. No tubercle bacilli had been found in the sputum. Bleeding and clotting time were normal, as was the sedimentation rate.

Examination.—This disclosed a thin, unusual-looking girl. The left side of her face was atrophic. The skin was café-au-lait color. On the left side of the face were many capillary angiomata. There was a cataract in the left eye. The thyroid was large, with a nodule on the left and diffuse enlargement of the right lobe. Some of the collected photographs reproduced by Carleton and associates [4] revealed a large thyroid gland, but no special comments were made about it. It was firm, not vascular, without bruit, and not as hard as one would expect a carcinoma to be. There was no sign of thyrotoxicosis. A nodule 15 mm. in diameter was felt in the right breast. A faint systolic murmur was heard to the left of the sternum in the second and third interspaces. There were no murmurs over the lungs, although the original suspicion of pulmonary arteriovenous fistula had led to a careful search. The lymph nodes were not enlarged. The abdomen appeared normal, and no organs or masses were felt.

Laboratory Studies.—The urine was normal. The hemoglobin was 13.5 gm. per 100 ml.; erythrocyte count, 5,090,000, and leucocyte count, 11,300 per cu. mm., with a normal differential count. X-rays of the chest demonstrated many round areas of increased density extending out irregularly from each hilum. They varied in size from 1 to 3 cm. An angiocardiogram failed to demonstrate arteriovenous fistulae. Bronchoscopic examination revealed no lesion, and the bronchogram was normal.

Course.—Soon after admission the patient suddenly developed severe abdominal pain and distention. Her right upper quadrant was especially tender, and a mass of indefinite margins was felt. Internal hemorrhage was suspected, since the hemoglobin fell to 5.5 gm. and the red cell count to 2,280,000. After a series of tranfusions the symptoms cleared and the mass could be felt no longer. When she was better, the thyroid was explored. A left hemithyroidectomy and biopsy of the right lobe was done. The left lobe appeared to be a hemorrhagic cyst. The right lobe contained four dark rounded masses which looked like hemorrhagic cysts, but the microscopic sections revealed a highly cellular tumor. Convalescence from the operation was uneventful. She was sent home. Subsequently she had several more bouts of hemoptysis and abdominal pain and other hospital admissions elsewhere. In the last week of life she had painful swelling of the right knee, left wrist, and left thumb. Three days before death she lapsed into coma and was paralyzed on the left side. She died at home Nov. 8, 1953, in spite of repeated transfusions and other supportive measures.

Postmortem Findings.—The lesion of the thyroid was the theme of much debate and speculation among our pathologists and those of the Armed Forces Institute of Pathology, the opinion being about equally divided between primary carcinoma and a vascular lesion with great proliferation of endothelial cells. Notes on the autopsy, obtained through the courtesy of Dr. F. C. Tucker, of Cedar Rapids, revealed these points of interest. The facial scarring and asymmetry were noted. A blue hemorrhagic nodule was seen under the skin over the left third rib at the anterior axillary line. Similar ones occurred below the right eye, on the nose, and at the right costovertebral angle. On dissection these nodules were grossly hemorrhagic. Hemorrhagic preaortic nodes were found. The kidneys, spleen, and adrenals were enlarged. The right adrenal weighed 150 gm., and the left, 155 gm. The liver was studded with many hemorrhagic nodules, some tiny, some ranging up to 5 cm. in diameter. Similar hemorrhagic nodules occurred

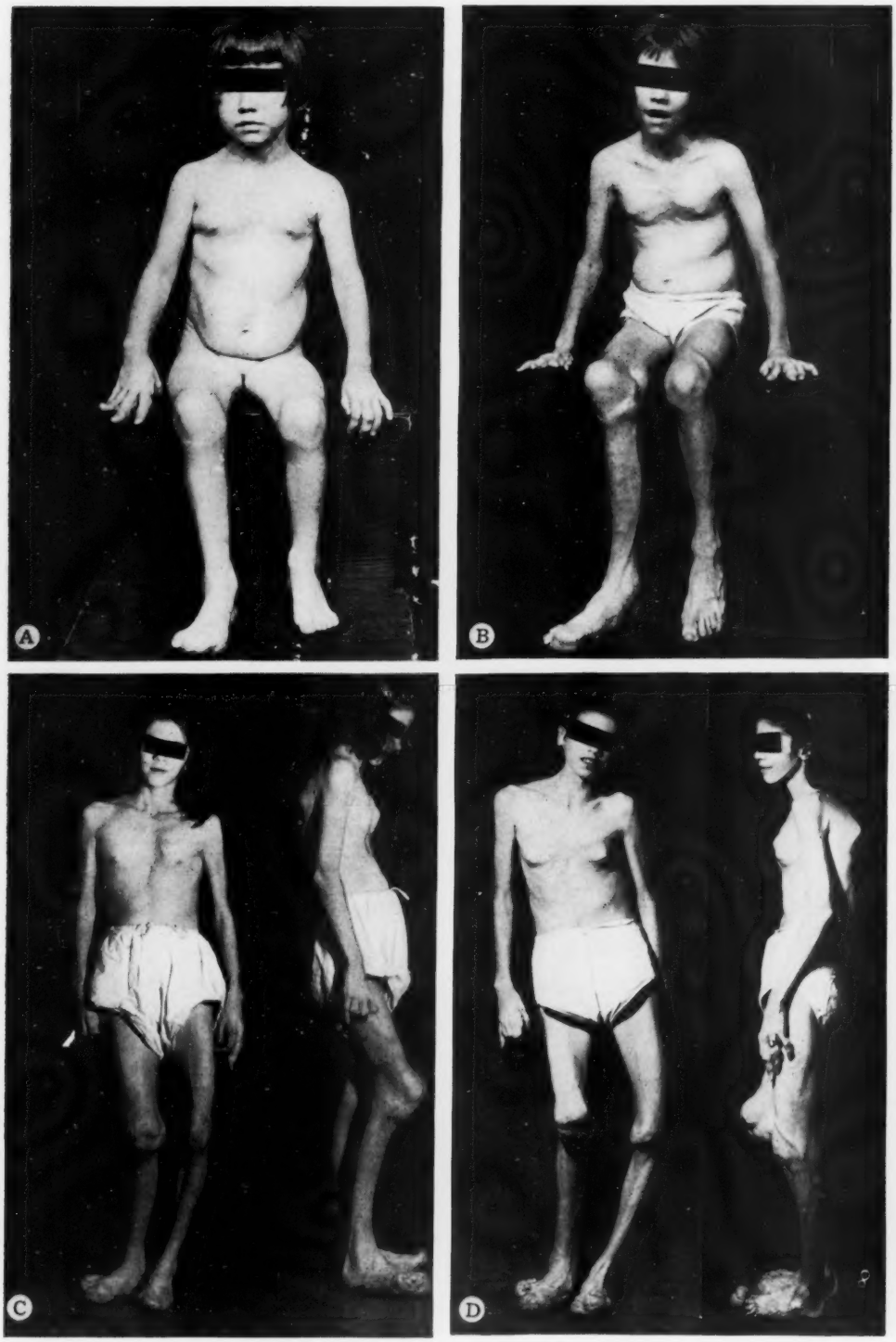

Fig. 1 (B. F., Case 2).—*A*, the patient at the age of 3 years. Early deformity of the right hand and foot is apparent. *B*, the progress of the disease by the 6th year. *C*, the status at age 11, illustrating bowing of the legs, the development of large veins in the lower legs without venous obstruction, and the asymmetrical warping of the skeleton. *D*, the status at age 15, illustrating the progress of the deformities.

beneath the parietal pleura. The lungs were full of similar nodules. In many the center was yellow, the periphery gray and hemorrhagic. The right sternoclavicular junction was enlarged, and the bone was softened. Nodules near the inferior vena cava penetrated its wall at the level of the left adrenal gland. A few nodules occurred in the pancreas and the ovaries. The thyroid contained the same sort of nodule. There was one in the calvarium on the left, over the parietal lobe of the brain, which was edematous and contained hemorrhagic and necrotic material. Section after fixation in formalin revealed an infarct in the right cerebrum at the level of the optic chiasm. Microscopic sections of the skin, adrenals, thyroid, breast, kidneys, lung, ovary, pancreas, lymph nodes, liver, and bone all revealed strands, islands, and sheets of endothelial-like cells surrounding irregular spaces containing red cells. The bone from the clavicle revealed osteochondroma. The final diagnosis was Maffucci's syndrome with (1) multiple hemangioma of the skin, (2) osteochondromata of the scapula and the clavicles, and (3) malignant changes of the hemangiomata with metastatic angiosarcoma of the skin, scalp, lungs, adrenals, liver, kidneys, lymph nodes, pancreas, thyroid, right ovary, and bone.

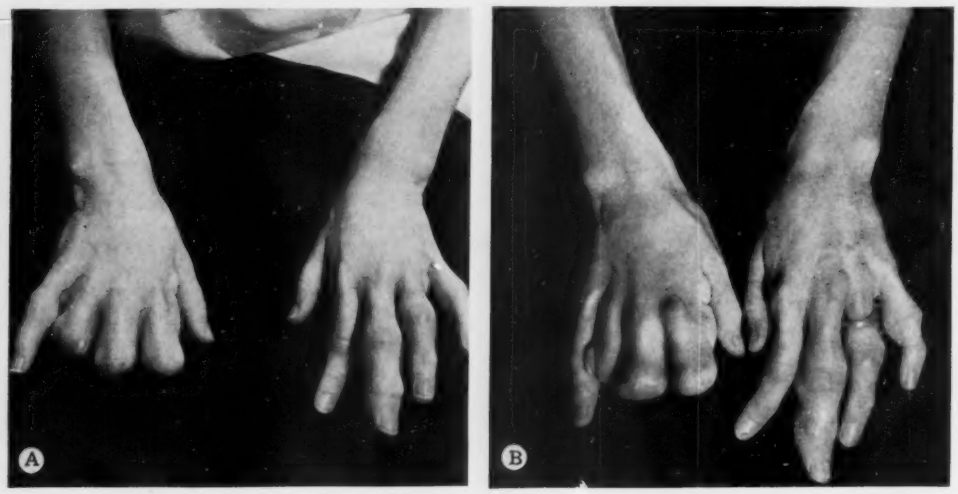

Fig. 2 (Case 2).—Close-up of the hands at (*A*) age 6 and (*B*) age 15.

Case 2.—B. F., a 17-year-old girl, has been attending one or another service of the University Hospitals for 15 years. She was born Oct. 28, 1937. Her parents were normal, the mother 21, the father 28 at the time of her birth. There was no consanguinity. The father's brother had died at the age of 2 with some congenital deformity of the spine which had prevented him from sitting up. An older brother and younger sister have always been normal. Gestation and birth of the patient was normal. She was breast-fed for 13 months. Not until she was 8 months old did her mother notice that the right hand was larger than the left. A little later the right leg and foot were noticed to be abnormally large. There was a slight limp. At the age of 2 years large veins were noted on the lateral aspect of the thigh and knees. When she was 33 months old the left middle finger had become larger than the others. When first examined at the University Hospitals she was 34 months old. Her general appearance is best observed in the photographs (Figs. 1 to 7). She was somewhat thin, with irregular enlargement of the right hand, leg, and foot and middle finger of the left hand. Behind the right ear was a still-draining sinus from a mastoidectomy. The right side of the face was slightly larger than the left. Cervical lymph nodes were enlarged. The abdomen revealed "soft fatty masses in the right upper quadrant of the abdominal wall and the lower left ribs anteriorly." The right leg was larger than the left. Range of movement was normal except for the right hip, where it was limited. There was grating of the right knee on moving. The right foot was large, the great toe bulbous, with large creases in the plantar surface, which was thick, wrinkled, and tender. The index, middle, and ring fingers of the right hand were gnarled, enlarged, and knobby, with limitation of movement. A diagnosis of hemihypertrophy was made.

During the next 14 years there were 17 admissions, mostly in an effort to correct and palliate the progressively distorting growth of bones of the extremities. A series of photographs illustrates better than words the cruel progress of the de-

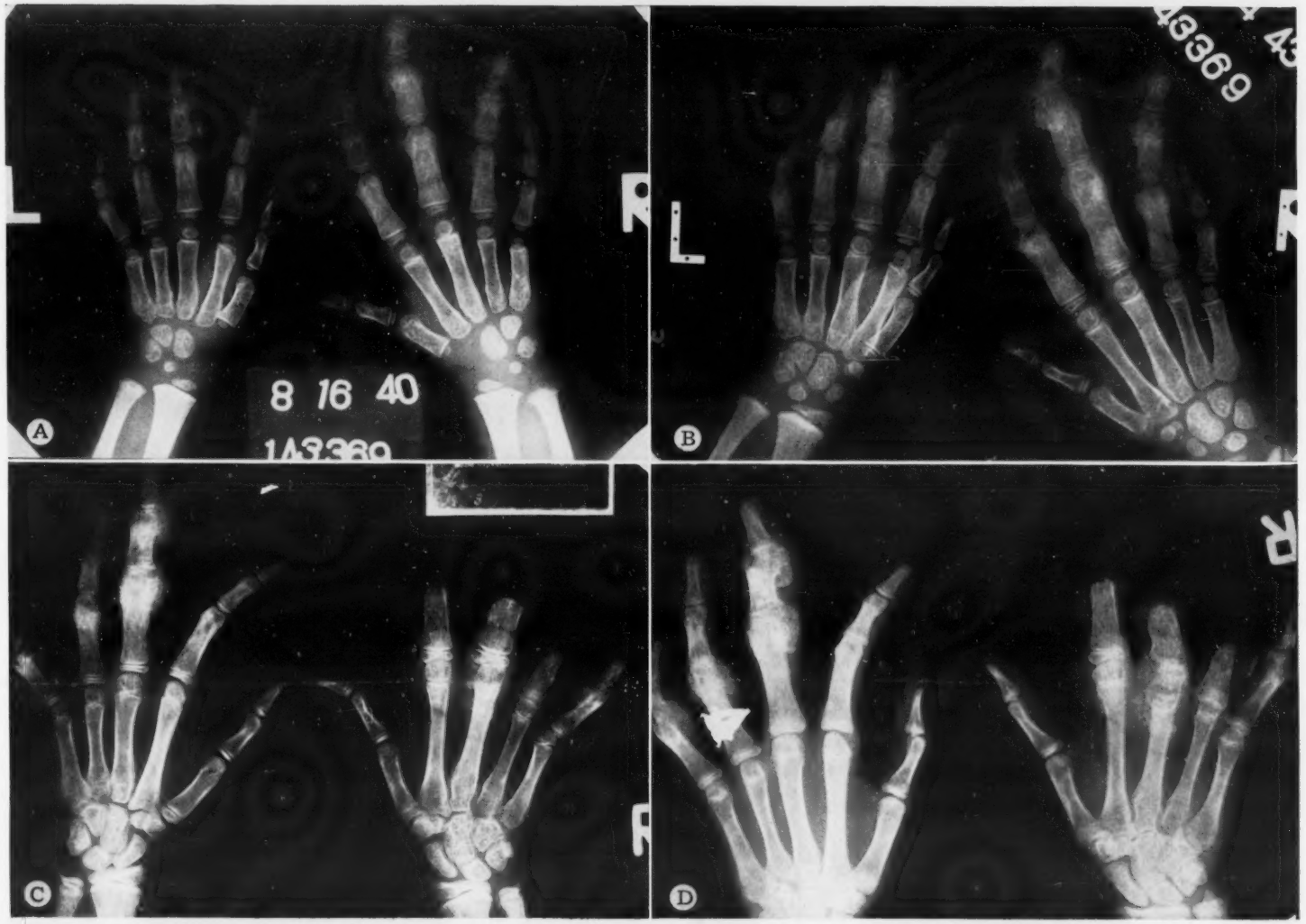

Fig. 3 (Case 2).—X-rays of the hands at ages corresponding to those in the parts of Figure 1. The pathological process is well established at the age of 3. The widespread occurrence of ostrochondromata, overgrowth of the bones, occurrence of calcification around the distorted metacarpophalangial junction of the third digit, the overgrowth of soft tissues, and the progressing deformity are demonstrated.

Fig. 4 (Case 2).—X-rays of the feet at the age of 6 years.

Fig. 5 (Case 2).—The feet at the age of 11 years. The cauliflower-like soft-tissue excrescences and enlargement of veins are well illustrated.

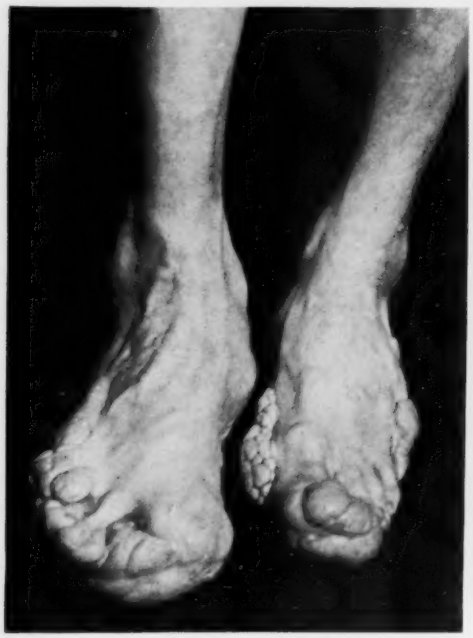

Fig. 6 (Case 2).—The deformity of the knees at (*A*) age 11 and (*B*) age 15 years.

A

B

C

Fig. 7 (Case 2).—The distortion of the right knee as it advanced from the age of 7 (*A*) and 11 (*B*) to 15 years (*C*).

formities and the modest results of repeated operations. In spite of her plight the girl has managed to make some adjustments and has kept up in school.

The following list outlines her hospital admissions and the progress of the disease for the period of observation.

March, 24, 1943: X-rays showed the enlarged bones to be osteoporotic. The great toe of the right foot was amputated, and epiphysial arrest was established in the distal femur and proximal tibia and fibula on the right. Wound healing and convalesence were normal.

Oct. 18, 1943: Admitted for several courses of x-ray therapy to the affected areas. The second, third, and fourth fingers of the right hand were amputated at proximal interphalangeal joint. The wounds healed per primum.

Jan. 10, 1944: Excision of redundant tissue of right foot.

Aug. 3, 1944: Return visit.

Jan. 3, 1945: Amputation of left little toe. Chronic otitis media. Microscopic examination showed a thick, horny layer over a thickened epidermis. The subcutaneous tissue was very thick and contained many sudoriferous glands. The bone of the phalanx was normal. Between the bone and subcutaneous tissue there was a thick layer of fibrocartilage without malignant characteristics.

April 26, 1945: Return visit. Healing complete. Shoe lift fitted.

April 25, 1946: Increasing valgus deformity of right ankle.

June 12, 1946: Return for shoe correction.

Aug. 27, 1946: Return visit. Continued slow increase in deformities. Complete skeletal survey

by x-ray revealed similar changes in bone structure in all sites of enlargement, with overgrowth of bone with hazy outlines and increased trabecular markings with a honeycombed appearance suggesting hemangioma. Treated for otitis media.

Aug. 5, 1949: Shoes adjusted.

Sept. 21, 1950: New shoes prepared.

March, 31, 1952: Return visit.

Aug. 22, 1952: Return visit.

Dec. 18, 1952: Return visit.

May 19, 1953: Return visit. Very little change.

Jan. 29, 1954: Return visit. No apparent change.

Fig. 8 (Case 3).—C. J. at the age of 10 months. The right upper quadrant mass, hemangiomata, and distortion of the foot are demonstrated.

March 15, 1955: Return visit. Slight progression of bony deformities.

Case 3.—C. J. was born of normal parents on Nov. 25, 1953. It was a twin birth, and his fraternal twin was normal. Both pregnancy and labor were in no way unusual. There was no family history of deformity or anomaly. The patient has been observed on three different admissions to the University Hospitals. Directly after his birth, his mother noticed discoloration of the skin of parts of the abdomen, back, both legs, and the right foot. The right foot was swollen and deformed. During his first hospital visit examina-

Fig. 9 (Case 3).—View from behind, showing the swollen right foot before operation.

Fig. 10 (Case 3).—Close-up of right foot after operation.

tion disclosed multiple hemangiomata of the skin, with soft swelling and deformity of the right foot and an asymmetrical mass superficial to the muscles of the right upper abdominal quadrant possibly communicating to the peritoneal cavity (Figs. 8, 9, and 10). Underneath this mass the edge of the liver could be palpated but did not seem to be unusual. Aspiration of this mass subsequently revealed clear fluid, and it was the general consensus that this represented a lymphangioma, although its nature has not yet been established certainly. Several operations on the foot have removed the angiomatous tissue and the hamartoma. The underlying bone seems to be normal except for the fact that the first and second metatarsals are larger than those of the left foot and there is some separation of these bones by the growing vascular mass, which had its origin in the region between them. None of the unusual angiomas pulsated or had bruits. An additional anomaly is an undescended left testicle.

In rate of growth, general appearance, and behavior this child has progressed as well as his brother. While it is not yet possible on the basis of the multiple anomalies to be absolutely sure that he has Maffucci's syndrome, he resembles many of the patients reported in the literature. The future progress of his numerous anomalies will enable us to settle this point at some time in the future. Presumably he falls into the classification of Maffucci's syndrome.

CASES REPORTED SINCE 1942

21.† Krause,[5] dyschondroplasia with hemangiomata. The patient was a 27-year-old U. S. Army soldier of Italian parentage. The family history was negative. He was bothered by a lump on his shoulder which pained him when he wore a pack. The lump had been present for 10 years. He was normal in development. There was no asymmetry, but his left side revealed a number of bony and vascular tumors. There were hard masses on the skin of the scapula and the third left costochondral junction. The second and third digits of the left hand were gnarled and deformed, and there were similar hard swellings on the dorsal surface of the left second and third metacarpals. Six soft bluish vascular tumors 1 to 3 cm. in diameter were scattered over the body on the left. The radiographic studies were interpreted as showing costochondromata of the third left rib and scapula, dyschondroplasia of the left hand and phleboliths in many of the hemangiomata. All the lesions were on the left.

22. Umansky,[6] dyschondroplasia with hemangiomata (Maffucci's syndrome). The patient was a 12-year-old Negro girl. At birth, four elevated dark blue masses were observed on the right leg. After the diagnosis of hemangioma, x-ray therapy was followed by regression of the lesions. Later, during the first year of life, two other nodules were excised. At the age of 6 the right thigh was larger than the left, and several large veins occurred at the site of the enlargement. Injection of the veins with sodium morrhuate did no good. At 8 the pelvis tilted because the right leg was shorter than the left and there was a slight limp. Venograms revealed a large venous hemangioma involving the right midthigh. It was excised along with more than two-thirds of the vastus lateralis muscle, which it had involved. Microscopically there were hemangiomatas and dilated venous spaces. The patient was discharged improved.

23. Kuzma and King,[7] dyschondroplasia with hemangiomatosis and teratoid tumor of the ovary. The patient was a 19-year-old girl of Polish descent. At the age of 5 she had bowing of the legs, especially of the left, and from 9 years on had several operations aiming to correct her deformity by stimulating or arresting epiphyseal growth. Nodules on the fingers of the right hand occurred at 14 years, and others soon appeared on the left hand. A large teratoid tumor of the ovary was removed when she was 19. At this time vascular tumors, radiolucent areas in the deformed bones, and soft tissue calcifications were noted. An amputated finger revealed young myxomatous cartilaginous tissue. The bluish nodules consisted of vascular spaces of varying cellularity resembling a cavernous hemangioma. The ovarian tumor, after much debate, was classified as a teratoma. For two years after the tumor was removed she did well, but enlarging nodular cystic areas appeared in the first, second, and sixth ribs on the left and in both shoulder girdles. Roent-

† These numbers continue the series of 20 cases recorded by Carleton and colleagues.[4]

genograms of the pituitary showed destruction of the sella. Three years after the ovarian tumor had been removed she died of extensive intra-abdominal metastases. There was no autopsy.

24. Strang and Rannie,[8] dyschondroplasia with hemangiomata. The patient was a 47-year-old woman whose parents were unrelated. No person in the family had any deformity. She was normal until the age of 7, when a broken leg failed to mend. At 11 lumps appeared on her hands and feet. They recurred after excision. In spite of her deformities she was able to support herself as a hairdresser and later as a milliner. Pain over the left eye had occurred spasmodically for a few days before she was admitted to the hospital in coma. She was grossly deformed, with a short bowed right leg, S-shaped tibia, and bulbous foot. The hands were gnarled and the fingers were knobby. There were many bluish tender tumors, and above her ankles there were multiple varices. The reticular pattern of fire stains marked the anterior surface of both legs. It is not known that she exposed them to or applied heat. Vascular tumors occurred in various parts of the skin. She died after classic signs of subarachnoid hemorrhage and right hemiplegia, after being in coma for a few days. Autopsy revealed multiple chondromata and a chondrosarcoma which was growing from the basisphenoid; it was necrotic and the site of massive hemorrhage. There were thrombosis of the cavernous sinus and necrosis of the pituitary gland. Cavernous angiomata were widespread. Some contained phleboliths. Many of the vascular tumors occurred in the snyovial membrane of joints. There was generalized phlebectasia.

25. Mullins and Livingood,[9] dyschondroplasia with hemangiomata. The patient was a 6-year-old Negro boy who had many lumps on his body. They had increased gradually in size since birth. Ten siblings were well, and no family history of similar trouble was known. The tumors were dome-shaped and fluctuant but fibrotic at the top. They did not pulsate. Biopsy was consistent with the diagnosis of cavernous hemangioma. X-rays of the bones revealed abnormal calcification and reduction in the size of the right humerus and forearm compared with the left. The left hemipelvis was smaller than the right. The left femur was bowed. Large dilated veins were seen above and below the hemangioma on the left leg. The hemangiomata were excised. The patient had not been seen again up to Feb. 9, 1955.

26. Nardell,[10] dyschondroplasia. A 34-year-old man was admitted to the hospital because of complications following amputation of the right leg. He had been normal at birth. At 5 a nodule was noted on the left hand, which was later fractured several times. A deformity of the right leg led to a series of amputations. Numerous large veins were noted over the deformed cartilaginous masses. The amputation site was fungating and sloughing. Biopsy revealed malignant lymphangioma, which had also been found at the time of the earlier amputation. He improved after x-ray therapy but later died of pulmonary metastases. There was no autopsy.

27. Halper and Wedlick,[11] Maffucci's syndrome. The patient was a 24-year-old woman. Her maternal grandmother has an angioma on the right side. The parents were normal, and so was the patient until the age of 3, when deformity of the hands was observed. She had many nosebleeds. At 5 an angioma in the left axilla was excised. Lumps appeared on the feet. From then on there were increasing deformities of many bones, new vascular tumors in the skin, and repeated fractures. When seen in 1946, she had widespread abnormalities of the dyschondroplastic type in the hands, forearms, sella turcica, and feet. She had severe genu valgum on the left. The fourth and sixth ribs had heavily calcified bodies near the costochondral junction. Typical enchondromata and eccondromata of the phalanges and metacarpals were found. Many phleboliths were found in the vascular tumors. In spite of the serious deformities, the patient was

able to work successfully as a telephone operator.

15. Tiwisina,[12] Case 15 of Carleton and associates.[3] Dyschondroplasia with multiple hemangiomas and local malignant changes (chondrosarcoma). This is a follow-up after a 16-year interval of Hellner's case, first reported in 1936. The family history was negative. At 7 years of age three hazel-nut-sized nodules developed on the right little finger. At 18 soft bluish nodules appeared on the palm and dorsum of the right hand and on the fingers. Later the fourth finger had to be amputated because of increasing deformity. The arm and, later, the foot and the right side of the chest became affected. Pain and swelling of the right foot and ankle joints led to amputation, which revealed a chondrosarcoma.

This report is illustrated with excellent reproduction of photographs, x-rays, and angiograms, which give a graphic indication of the extent and severity of the lesion.

COMMENT

The main problems posed by Maffucci's syndrome concern the relationship between the disorders in two separate tissues. Does the vascular lesion determine the dyschondroplasia, or are the two produced by some other mechanism, probably a genetic one? Without recapitulation of all the evidence Carleton and her associates [4] brought out, the asymmetry of the vascular lesions and cartilaginous lesions demonstrates that the localization of the lesions in the same place is not obligatory, that their concurrence is probably coincidental rather than consequential. Any idea about genetic mechanisms is speculative, but most probably multiple effects of a single gene are responsible. Perhaps subsequent developments in our third patient will cast some light on the matter. Patients with only dyschondroplasia (Ollier's disease) or only vascular hamartoma should be studied for disorders of the other, apparently unaffected tissues. Umansky's observations suggest that only 1 in 50 to 100 persons with either type of lesion might be expected to have the other also.[6]

The experience recorded here permits the extension of generalizations already made and the suggestion of others. First, the disease may be suspected very early in life when unusual hemangiomata of the skin do not regress or disappear. In childhood the dyschondroplastic disorder may cause various deformities and pathological fractures. In any dysplastic anomaly, mild examples, formes frustes, are overlooked until the classic form is familiar. The occurrence of three cases in one hospital suggests that this rare disease is not so rare as the small number of case reports would suggest. The fact that a diagnosis was finally made in two of the patients after they had been observed for many years demonstrates that we see not what we look at but what we look for. In my own experience, finding rare diseases has resulted from being familiar with them and looking for them.

The several kinds of malignant tumors to which different victims of Maffucci's syndrome have succumbed—chondrosarcoma (four), angiosarcoma (one), malignant lymphangioma (one), glioma (one), and ovarian teratoma (one)—demonstrates the very high risk of malignant neoplasm.

The disorder has been reported in widely separated regions—England, Germany, Australia, and several parts of the United States. It has been reported in Negroes and in those of Anglo-Saxon, Polish, and Italian stocks. With increased familiarity we may expect that it will be recognized at an earlier age. These three cases suggest that Maffucci's syndrome is less rare than the case reports indicate.

SUMMARY AND CONCLUSIONS

Three new cases of Maffucci's syndrome are reported. This brings the total to 30.

The syndrome is commoner than the recorded cases suggest.

The curious association of dyschondroplasia and hemangiomata, the devastating deformity which makes the victim a tragic caricature, the high incidence of malignant neoplastic change all challenge the geneticist, the practicing physician, and the cancer spe-

cialist to provide a better understanding of this disorder.

Any advance depends on recognizing the disorder. This is ample reason for calling attention to it.

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Experimental Pseudomembranous Enterocolitis

Production by Means of Thrombosis of Intestinal Mucosal Capillaries

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During the course of some animal experiments designed to elucidate the functional and pathologic effects of incompatible blood transfusion, it was observed that under certain experimental conditions the syndrome of pseudomembranous enterocolitis occurred. In considering these experiments it was noted that there was a striking similarity between the cases described in the literature and the syndrome produced in the dog. For the purpose of comparison with the animal experiments a brief résumé of the essential features of the human cases will be presented first.

Clinically, the disease is manifest by the sudden appearance of irreversible shock, nausea and vomiting, diarrhea (sometimes bloody or tarry stools), cramping abdominal pain with distention, passage of membranous shreds per rectum, fever, oliguria, neurological symptoms, and severe loss of fluid and plasma protein, with death usually in a few hours.* Uremia often develops in patients who survive the initial period of shock, while some patients may recover completely.[3] The syndrome appears most commonly postoperatively, and usually following abdominal surgery for carcinoma of the colon. Nevertheless, it has been observed in patients who have not been operated on but who had (1) neoplastic obstruction of the large intestine, (2) cardiac disease, and (3) infection. A wide variety of surgical and medical conditions precede the onset of this disease process.[4]

Pathologically, the outstanding changes are found in the gastrointestinal tract.† The lesion may be located at any level, from the esophagus to the colon, but the small intestine and the colon are most frequently involved. The process may involve the entire intestinal mucosa or may show "skip" areas. The typical macroscopic appearance is that of a loose pseudomembrane overlying an eroded and congested mucosa. With increasing severity of involvement, hemorrhagic phenomena appear. Microscopically, the pseudomembrane is composed of fibrin, leucocytes, disintegrated red blood cells, mucus, epithelial cells, and bacterial colonies. The superficial mucosa is necrotic, and the mucosal connective tissue is filled with extravasated red blood cells and edema fluid. The superficial capillary vessels of the mucosa are dilated, and many observers have described hyaline thrombi in some areas in these vessels. The submucosa as well as the deep portion of the mucosa is usually intact, although rarely the necrosis may extend deep enough to allow perforation of the bowel.

The pathogenesis of this lesion has been explained by a variety of concepts. Billroth [7] gave the first recognizable description of the disease in 1867. After an unsuccessful attempt to remove a large goiter, his patient developed melena and died with multiple ulcerations in the duodenum. Although there was no direct evidence for it, Billroth attributed these changes to sepsis. Von Eisels-

Aided by a grant from The Office of The Surgeon General, United States Army, Project 6-60-01-002.

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* References 1 and 2.

† References 5 and 6.

berg [8] described similar lesions in the stomach and duodenum in postoperative fatalities, and he considered that retrograde emboli from thromboses in the omentum had caused them. Busse [9] and von Winniwarter [10] subscribed to the same thesis. Klemperer, Penner, and Bernheim [11] suggested the concept that the common pathogenetic factor responsible for this lesion is shock, with its attendant arteriolar vasospasm as the cause of mucosal necrosis. The most recent idea concerning the etiology of this disease has been that antibiotics are in some way responsible.‡ In general, this concept envisions a superficial mucosal infection as the essential feature of the disease. The inflammation due to infection is presumed to result from an alteration of the intestinal flora by the antibiotic. Many antibiotics have been incriminated, and no specific organism has been held responsible. It is important to note that according to Pettet [2] the disease is no more prevalent now than it was in the days before antibiotics were in use, which casts considerable doubt on this hypothesis.

It is the purpose of this report to present the evidence from animal experiments that the cause of pseudomembranous enterocolitis is intravascular clotting in the mucosal capillaries of the gastrointestinal tract during a period of so-called "compensated" shock.

MATERIALS AND METHODS

Seven mongrel dogs of both sexes were anesthetized with 300 to 420 mg. of pentobarbital sodium intravenously. The left femoral artery was exposed, and a 10 cm. left rectus abdominal incision was made. A polyethylene catheter was next inserted into the aorta by way of the femoral artery so that the tip lay 2 cm. above the renal arteries. Human bank blood was then forced through the catheter under pressure by means of an arterial transfusion set. The amount of blood varied from 120 to 300 ml., and the duration of injection varied from 5 to 47 minutes. The catheter was withdrawn, and the femoral artery was ligated. The left kidney was then freed, and wedge biopsy specimens were taken of the renal cortex tissue at 15, 30, and 45 minutes; 1 hour, and 2 hours after completion of the transfusion. At the three-hour interval a left nephrectomy was performed and the abdominal incision was closed. This part of the procedure was varied to the degree that the nephrectomy was done at one, one and one-half, and two hours in three of the experiments. Hemostasis at the renal biopsy site was poorly achieved by mechanical pressure, and, because of the hypocoagulability of the blood, a considerable amount of blood was lost from the animals' circulation at this point. The blood loss varied, but in general it amounted to 100 to 150 ml. Autopsies were performed immediately after death, and the tissues were fixed in 10% formalin and in Zenker's solution and stained with hematoxylin and eosin and phosphotungstic acid hematoxylin.

‡ References 12 and 13.

RESULTS

CASE 1.—Dog 9 was given 120 ml. of incompatible blood over a period of 33 minutes. A left nephrectomy was performed one and one-half hours after the transfusion. The animal's pulse and respiration increased shortly after the start of the transfusion. A copious bloody diarrhea developed four and one-half hours later. The dog remained anuric and unconscious until it died in progressive shock, six and one-half hours after the experiment was started.

Autopsy.—Gross: Stomach contained 150 ml. of blood-tinged mucus. Duodenum, jejunum, and ilium lined by a hemorrhagic mucosa and filled with blood. Terminal ileum free of hemorrhage. Colon filled with blood and lined by hemorrhagic mucosa.

Microscopic: Small bowel and colon: Numerous thrombi in mucosal vessels with superficial necrosis of mucosa and pseudomembrane on surface. Kidneys: Capillary thrombi in biopsy specimens. Focal tubular necrosis in autopsy specimen.

CASE 2.—Dog 12 received 215 ml. of incompatible blood in 47 minutes. Left nephrectomy was performed at the end of three hours. Pulse and respirations became rapid soon after the injection was started. The dog remained anuric, vomited terminally, and died in progressive shock six hours after the experiment was started.

Autopsy.—Gross: Few pleural petechiae. Small bowel mucosa congested. Numerous petechiae on colonic mucosa.

Microscopic: Lung: Focal intra-alveolar hemorrhage and atelectasis. One or two thrombi in small pulmonary vessels. Small bowel: Mucosal capillaries dilated and congested. Colon: Numerous thrombi in mucosal vessels with superficial necrosis of mucosa. Kidney: Thrombi in capillaries in biopsy specimens. Foci of tubular necrosis in autopsy specimen.

CASE 3.—Dog 14 was given 300 ml. of incompatible blood in 30 minutes. The left kidney was removed at the end of three hours. The pulse and respiration rate increased shortly after the blood was started. The dog remained anuric until it died

in progressive shock, five and one-half hours after the start of the experiment.

Pathology.—Numerous thrombi were found in the capillaries of the kidney in the biopsy and nephrectomy specimens.

CASE 4.—Dog 16 received 200 ml. of incompatible blood in 15 minutes. There was a continuous oozing of blood from the edges of the abdominal incision. The animal remained anuric and unconscious until it died in progressive shock, seven hours after the start of the experiment.

Autopsy.—Gross: Hematoma in subcutaneous tissue adjacent to incision; 100 ml. of fluid blood in peritoneal cavity. Large subendocardial hemorrhage in left ventricle of heart. Numerous petechiae and ecchymoses on pleural surfaces. Petechiae on serosal surface of stomach. Small bowel: Areas of mucosal hemorrhage approximately 5 to 7 cm. in length alternating with "skip" areas of normal pink mucosa. Hemorrhages present throughout entire length of small bowel. Colon: Hemorrhagic mucosa.

Microscopic: Heart: Subendocardial hemorrhage. Focal pulmonary intra-alveolar hemorrhage and atelectasis. Liver: Platelet thrombi in central veins and hepatic arterioles with central congestion and early necrosis of liver cells. Small bowel: Few thrombi in mucosal capillaries with associated hemorrhage and necrosis. Colon: Numerous thrombi in mucosal capillaries with superficial necrosis of mucosa. Adrenals: Focal cortical hemorrhages. Kidney: Capillary thrombi in biopsy specimens.

CASE 5.—Dog 17 was injected with 125 ml. of incompatible blood in nine minutes. The left kidney was removed at the end of two hours. The pulse and respiration rates increased after administration of the blood. The animal remained anuric and unconscious until it died in progressive shock, two and one-half hours after the experiment was started.

Autopsy.—Gross: Focal atelectasis of both lower lobes. Numerous 5 mm. mucosal and serosal hemorrhages over cardia of stomach. Small bowel: Congestion of entire mucosa with 20 cm. segment of hemorrhagic mucosa in ileum and blood in lumen. Colon: Numerous hemorrhagic patches in mucosa.

Microscopic: Focal pulmonary atelectasis. Liver: Few thrombi in hepatic arterioles. Small and large bowel: Numerous thrombi in mucosal capillaries with focal superficial hemorrhage and necrosis.

CASE 6.—Dog 18 received 125 ml. of incompatible blood in 13 minutes. Left nephrectomy was performed three hours after the transfusion was completed. The animal remained anuric until it died in progressive shock, three hours after the experiment was started.

Autopsy.—Gross: Small bowel: Numerous irregular patches of hemorrhagic mucosa alternating with normal pink mucosa.

Microscopic: Heart: Subendocardial hemorrhage. Lungs: Focal atelectasis. Small bowel: Dilated congested mucosal capillaries with hemorrhage into villous stroma. Colon: Numerous thrombi of mucosal capillaries with little or no hemorrhage or necrosis. Kidney: Numerous thrombi in renal capillaries in biopsy specimens.

CASE 7.—Dog 52 was dehydrated for four days preceding the experiment. This animal received 125 ml. of incompatible blood in five minutes. The left kidney was removed one hour after the experiment was started. Rapid pulse and forced respirations appeared soon after the transfusion began. Anuria persisted and the animal was unconscious until it died in progressive shock, 10½ hours after the transfusion was completed.

Autopsy.—Gross: Forty milliliters of fluid blood in peritoneal cavity. Foci of pulmonary atelectasis. Liver: Surface mottled with large yellow-orange areas alternating with dark red-brown patches. Some yellow areas extend into substance of liver. Small bowel: Entire mucosa hemorrhagic and lumen filled with bloody mucus. Sharp line of demarcation between normal pink pyloric mucosa and hemorrhagic mucosa of duodenum. Pseudomembrane on mucosal surface of 20 cm. segment of ileum. Colon: Mucosal petechiae and pseudomembrane.

Microscopic: Pulmonary atelectasis. Liver: Periportal and central congestion. Small bowel: Hemorrhagic necrosis of superficial portion of mucosa. Numerous large masses of extravasated fibrin at tips of villi. Pseudomembrane on mucosal surface consisting of masses of desquamated epithelial cells, mucus, fibrin, and polymorphonuclear leucocytes.

COMMENT

A. ANIMAL EXPERIMENTS

The essential "clinical" changes induced in the dogs by this experimental procedure consisted of (1) progressive shock, (2) death within several hours, (3) anuria, (4) coma, and, rarely, (5) bloody diarrhea. The essential pathologic changes were (1) hemorrhagic necrosis of the superficial mucosa of the gastrointestinal tract, (2) pseudomembrane formation in the jejunum and ileum, (3) thrombosis of the capillaries of the mucosa of the intestinal tract, (4) thrombosis of capillaries of the kidney, and, rarely, (5) microscopic thrombi in pulmonary and hepatic capillaries.

The hemorrhagic necrosis of the superficial mucosa is caused by the multiple capillary thromboses in the intestinal mucosa. The

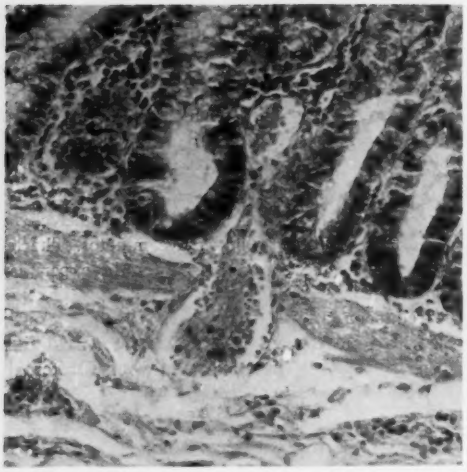


Fig. 1 (Dog 18).—Colon. Thrombus in capillary traversing muscularis mucosae. This is the earliest histologically detectable change in the experimental production of pseudomembranous enterocolitis. Hematoxylin and eosin; reduced from mag. × 240. (Walter Reed Army Hospital, AMH 15368, A)

Fig. 3 (Dog 16).—Ileum. The mucosa on the right is intact. The superficial portion of the mucosa on the left is necrotic and hemorrhagic. One capillary thrombus is visible in the mucosa of the hemorrhagic area in this low-power photomicrograph. Hematoxylin and eosin; reduced from mag. × 50. (Walter Reed Army Hospital, AMH 15368, F)

stages of development of these lesions can be traced histologically in these experiments. The earliest change is thrombosis of the capillaries which, at the outset, is unassociated with necrosis (Figs. 1 and 2). However, in a very short time the mucosal tissue distal to the thrombi undergoes infarct necrosis, with hemorrhage into the connective tissue of the villi and into the lumen of the intestine (Figs. 3 and 4). In time the mucosal surface is covered with a layer of necrotic, disintegrating glandular epithelial cells from the infarcted superficial mucosa, fibrin, mucus, red blood cells, and polymorphonuclear leucocytes (Figs. 5-10). The development of necrosis is a very rapid process, since it

Fig. 2 (Dog 18).—Colon. Thrombus in mucosal capillary. This is an early lesion, since necrosis has not yet occurred. Hematoxylin and eosin; reduced from mag. × 240. (Walter Reed Army Hospital, AMH 15368, B)

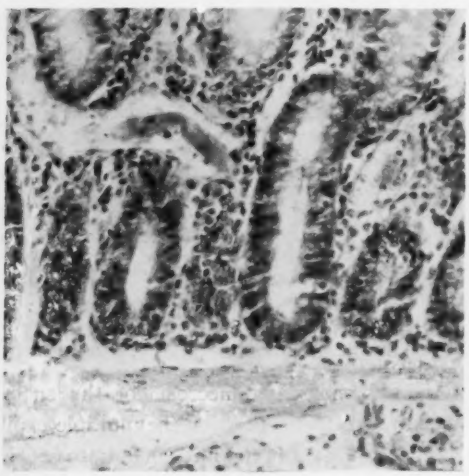


Fig. 4 (Dog 16).—Ileum. Higher-power view of area shown in Figure 3. Hematoxylin and eosin; reduced from mag. × 110. (Walter Reed Army Hospital, AMH 15368, E)

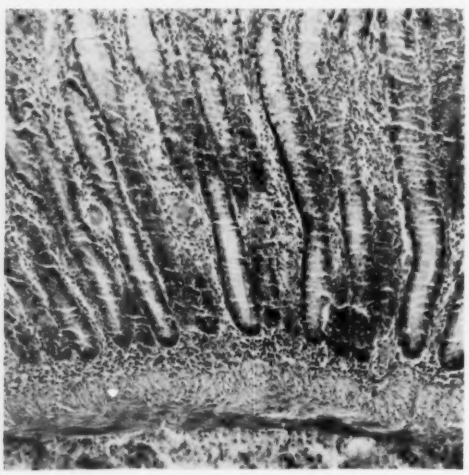
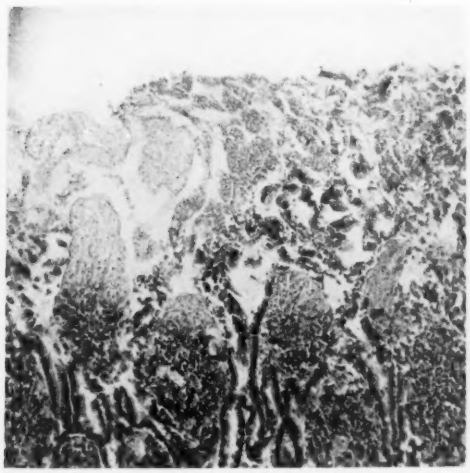


Fig. 5 (Dog 17).—Jejunum. The deeper portions of the mucosa are intact, but the tips of the intestinal villi are necrotic and the superficial epithelium has peeled off in chunks. Hematoxylin and eosin; reduced from mag. × 50. (Walter Reed Army Hospital, AMH 15368, G)

was observed in one animal two and one-half hours after the transfusion was started. The thrombi appear practically instantly. This fact was best demonstrated in experiments described elsewhere,§ in which animals died in a matter of minutes after the transfusion, with numerous thrombi in various

§ References 14 and 15.

Fig. 6 (Dog 17).—Jejunum. Higher-power view of area shown in Figure 5. Hematoxylin and eosin; reduced from mag. × 110. (Walter Reed Army Hospital, AMH 15368, D)



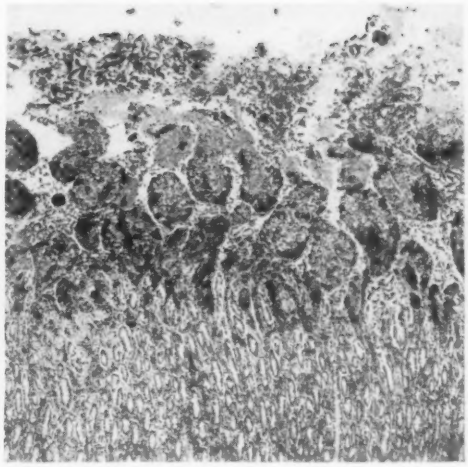
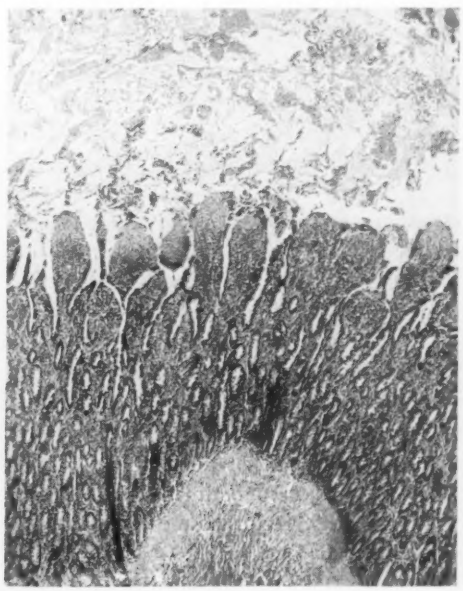


Fig. 7 (Dog 52).—Jejunum. The dark patches in this photomicrograph are masses of red blood cells. The tips of the villi are necrotic and large masses of fibrin lie free in the lumen, surrounded by epithelial cells and leucocytes. This is the beginning of the formation of the pseudomembrane. Hematoxylin and eosin; reduced from mag. × 50. (Walter Reed Army Hospital, AMH 15368, J)

Fig. 8 (Dog 52).—Jejunum. The pseudomembrane is fully developed in this region and is composed of strands of fibrin, mucus, and desquamated epithelial cells. The tips of the villi are necrotic and hemorrhagic. Hematoxylin and eosin; reduced from mag. × 50. (Walter Reed Army Hospital, AMH 15368, H)



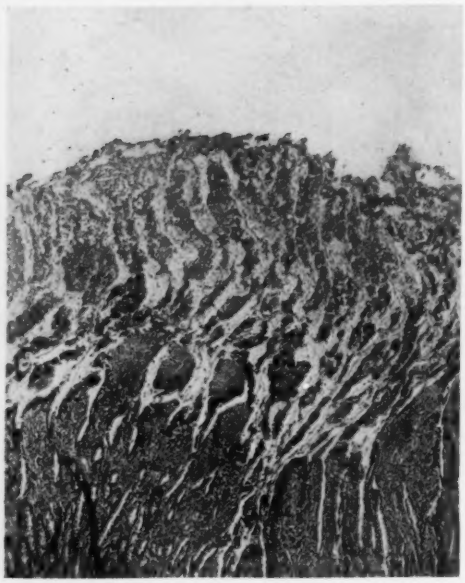


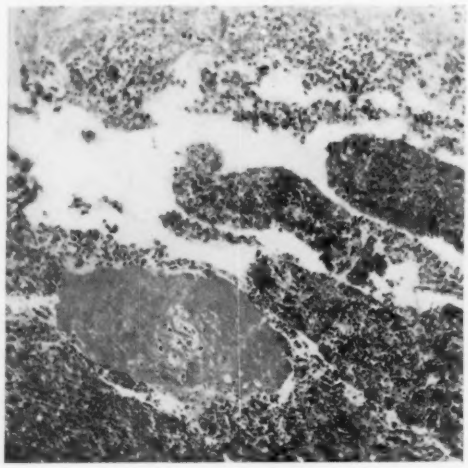
Fig. 9 (Dog 52).—Jejunum. Superficial portion of mucosa with overlying pseudomembrane. Hematoxylin and eosin; reduced from mag. × 50. (Walter Reed Army Hospital, AMH 15368, I)

organs. Further evidence that the thrombi form instantly was obtained when the superior mesenteric artery was manually occluded during the administration of the incompatible blood and then released. None of these animals developed intestinal mucosal thrombi or pseudomembranes. These experiments will be reported subsequently.

The cause of the intravascular thrombi lies in the administration of incompatible blood. This has been demonstrated hematologically and anatomically.‖ The precise mechanism by which incompatible blood produces intravascular clotting is unknown, but the most promising lead in this regard is that the hemolyzed red blood cells release a factor that induces clotting. Quick[17] has demonstrated such a material from hemolyzed human red cells in in vitro experiments.

While it seems clear that the thrombi are primarily responsible for the sequence of events that leads to pseudomembranous enterocolitis in these experiments, it is equally clear that some factor besides the intravascular clotting episode is necessary to cause the localization of the thrombi in this region. This fact was demonstrated in previously reported experiments in which incompatible blood was transfused into the aorta of dogs without submitting them to laparotomy or repeated renal biopsy.[15] In these experiments there was clear-cut histologic evidence that intravascular clotting had occurred, but it took place in the liver, spleen, and kidneys and not in the gastrointestinal tract. The only difference between the two experiments is that currently a laparotomy preceded the intra-aortic transfusion and was followed by repeated renal biopsies and unilateral nephrectomy. The surgical trauma of these procedures apparently was in some way responsible for localizing the thrombi in the intestine. In terms of functional alterations, it is well known that surgical trauma causes "compensated" shock, which is associated with arteriolar constriction and capillary dilation in the splanchnic bed.[18] It seems likely that this stasis of blood in the splanchnic capillaries is in part responsible for localizing the thrombi in this region. This is reasonable when it is recalled that the stasis of blood in larger vessels such as leg veins is partially responsible for localizing macro-

Fig. 10 (Dog 52).—Jejunum. High-power view of necrotic tips of intestinal villi and large mass of extravasated fibrin. Hematoxylin and eosin; reduced from mag. × 110. (Walter Reed Army Hospital, AMH 15368, K)



‖ References 14-16.

scopic thrombi in these large vessels. The same mechanism may be in operation on a microscopic scale in the case of the capillary thrombi.

In summary, these experiments indicate (1) that pseudomembranous enterocolitis can be induced experimentally in dogs, (2) that the trigger mechanism that sets off the reaction is an episode of intravascular coagulation, (3) that pseudomembranous enterocolitis under these conditions is caused by numerous thrombi in the capillaries of the intestinal mucosa, and (4) that the localization of the thrombi in the intestine is conditioned in part by a state of "compensated" shock due to surgical trauma and associated with stasis of blood in the splanchnic capillary bed.

B. Comparison with Pseudomembranous Enterocolitis in Man

From the functional standpoint there is a striking similarity between the animal experiments and the clinical aspects of the disease in man. They share in common irreversible shock, coma, anuria, and death within a few hours of the onset of the disease. Bloody diarrhea occurs occasionally in both. The disease appeared after operative intervention in the dogs and is most frequently seen as a postoperative complication in man. One point of difference is the presence of watery diarrhea in over 40% of the human cases. This was not observed in any of the animal experiments. Also, a few patients have survived this condition, whereas none of the dogs did. However, it should be noted that none of the dogs were treated with compatible blood, plasma, or intravenous fluids, which may be life-saving agents in the human patients who survive.

From the pathological standpoint, the lesions produced in the dogs are identical to those observed in human cases. Both exhibit pseudomembranes, patchy or diffuse involvement of the intestinal mucosa (more commonly in the colon and small intestine), superficial mucosal hemorrhage and necrosis, and thrombosis of the mucosal capillaries. Also, Penner has called attention to the fact that, in addition to the intestinal lesions, focal necrosis in the liver, pancreas, and kidneys can be found in human cases. Similar lesions were observed in the dogs. One pathologic difference between the dog lesions and the descriptions of the human cases lies in the presence of bacterial colonies in the pseudomembrane of the human cases. This may be merely a matter of time, since postmortem growth of bacterial colonies in man could explain this difference. On the dogs autopsy was done immediately after death, while the average human autopsy is not done for several hours after death. We subscribe to Penner's thesis that any bacterial inflammation in these cases is secondary to the ischemic necrosis of the mucosa.

The similarity of these experiments to the case reported by Thoma and Smoot [19] deserves emphasis. These authors described the case of a 9-year-old patient with a three-day history of abdominal pain and distention with nausea and vomiting due to intestinal obstruction from a fibrous adhesion. The boy developed sudden irreversible shock, copious bloody stools, and fever and died 30 hours after admission. At autopsy the mucosa of the small intestine was hemorrhagic. The process was limited sharply to the small intestine, beginning at the pylorus and ending abruptly at the ileocecal valve. Bloody diarrhea and involvement of the entire small bowel mucosa by hemorrhagic necrosis, with a sharp line demarcating normal pyloric mucosa from the hemorrhagic duodenum were observed in one of the animal experiments (Dog 52).

C. Pathogenesis of Pseudomembranous Enterocolitis in Man

The question of how much of these animal experiments can be carried over toward an explanation of the human disease remains to be answered. Since the lesion in the animal is identical to that in man, a close comparison may be made, and it seems likely that the process in both instances is initiated by an episode of intravascular coagulation with thrombosis of the intestinal mucosal capillaries. The cause of intravascular clotting

in the dogs is the incompatible transfusion reaction. However, we have found no reference to such an etiologic agent among human cases. Therefore, some other source or precipitating factor for the intravascular clotting episode must be sought. The commonest condition preceding the onset of this syndrome is operative intervention for carcinoma of the colon. Carcinoma is well known for its association with episodes of intravascular coagulation. While it is generally recognized that thromboses of large vessels, including at times the vena cava, are not uncommon, it is not as generally known that disseminated capillary thrombi may also be found in patients dying of cancer. We have observed one patient with carcinoma of the pancreas with disseminated microscopic thrombi in the liver and spleen,[20] and one patient with carcinoma of the cervix with innumerable capillary thrombi in the kidneys.[21] Carcinoma of the colon is also associated with disseminated microscopic thrombi. An example of this is a recent case of carcinoma of the colon with fibrinous vegetations on the heart valves and numerous microscopic thrombi in small vessels of the heart, lungs, and liver. These cases supply the information that episodes of diffuse intravascular coagulation do occur in patients with carcinoma.

Therefore, the two conditions necessary for the appearance of the syndrome of pseudomembranous enterocolitis in animals can be found in these human cases of surgical intervention for carcinoma of the colon. These are (1) an episode of intravascular coagulation with (2) operative trauma causing the thrombi to localize in the intestinal mucosal capillaries.

More information concerning the state of the intestinal capillary bed and the hematologic findings in the cases preceded by sepsis and cardiac disease will be necessary before a similar comparison can be made in such instances.

SUMMARY

Pseudomembranous entercolitis has been produced experimentally in dogs by the administration of incompatible blood into the aorta with concomitant surgical trauma consisting of laparotomy, repeated renal biopsies, and left nephrectomy. The intestinal lesions are caused by thrombosis of capillaries of the intestinal mucosa. The thrombi are the result of two conditions, (1) intravascular clotting and (2) "compensated" shock with arteriolar constriction and pooling or stasis of blood in the dilated splanchnic capillaries. The clinical syndrome and pathologic lesions in the animals are similar to those in pseudomembranous enterocolitis in man. It is suggested that the pathogenesis of the lesion in man depends on the same two factors, i. e., intravascular coagulation and stasis of blood in the intestinal mucosal capillaries.

Cpl. Robert Burns and Cpl. Jack Taylor gave technical help in conducting these experiments.

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Hereditary Tremor

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and
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In 1860, a Great Lakes ship captain migrated to Utah. This man is reported to have had a severe tremor during the last 20 years of his life. The present study is concerned with the characteristics and incidence of the tremor among four generations of his descendents, 24 of whom have been examined. Most reports on familial tremor describe the clinical findings observed in a few afflicted members from several unrelated families. Reliance is placed on the family history as presented by the patients for data about the incidence of this trait among other members of the family. As is illustrated in this report, such information may be unreliable as regards the frequency of occurrence of tremor in the progeny.

Examination of the subjects usually was made in their homes, which lie within a radius of 40 miles of Salt Lake City. With the exception of the propositus (III-19), who was seen in the outpatient department, selection of persons examined was related only to their geographical distribution. All available members of the kindred were examined, whether information from other sources indicated that they had a tremor or not. In each instance efforts were made to obtain a detailed family history of tremor. In addition, the subject was questioned regarding any tremor in himself and about other difficulties, particularly those relating to the nervous system. The answers to these queries varied. Most of the family were cordial and cooperative. Certain family members had good insight regarding the presence of this condition in themselves and in their immediate relatives. Others seemed unaware of its hereditary character. A few, in whom shaking of the head and hands was evident during the interview, denied the presence of tremor. Only one person was openly hostile. Even the more tractable persons, however, often were unwilling to have their children examined by us.

The examination of the subjects was restricted to certain specific procedures. The gait was observed, and the Romberg test was carried out. Search was made regarding the presence of rigidity of the arms and legs. Tests to indicate adiadokokinesis and the cerebellar rebound phenomenon were made. Extraocular movements were observed, and nystagmus was sought for. Efforts were made to detect tremor in the voice, head, arms, and hands. The hands were examined at repose on a table, when outstretched with extended arms, upon execution of the finger-to-nose maneuver, and upon opposition of the subject's finger with that of the examiner. Small glass beads were scattered about a flat surface, and the subjects were instructed to pick them up as quickly as possible. A sample of handwriting was obtained.

The histories of those who were aware of their tremors showed certain similarities. It usually was not possible to date the onset of the tremor to any age in life. Terms such as "all my life," "since childhood," and "since I was twenty" were applied frequently. All subjects were right-handed, and all thought the tremor to be worse in the left hand. Two persons with severe involvement indicated that shaking had become worse after the age of 50 years. All were aware that emotion aggravated the disorder. They usually reported that it was difficult to drink liquids

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from a full container in the presence of many people. Another common complaint related to their tremulous handwriting while being observed, as by a teacher at school or by a banker while signing a note. Women with the tremor had no difficulty in threading needles. Several persons with severe shaking of the hands and head acknowledged that they choked frequently while drinking liquids. No one was aware of any disturbance of walking. Of the 19 persons found, upon examination, to have tremor, none could be regarded as incapacitated. In two men over 70 years of age, writing, shaving, and buttoning their clothes were not easy. Of the two, however, one had killed a deer with a rifle at 200 yards the previous autumn.

A few minor incidents serve to supplement the nature of the tremor in this family. One person, an electrician, could not use a screw driver when someone was watching him but did well when alone. A young male adult applied to the Air Force and was rejected when a tremor was detected. When he reapplied, he brought his father along for reassurance and was accepted for pilot training. A locomotive engineer thought the tremor was most evident when he extended his left arm to grasp the throttle.

Relatively few of the entire family indulged in coffee, tea, or tobacco. Those who did had not noticed whether or not these agents enhanced the tremor. Ten persons were aware that small to moderate amounts of alcoholic beverages lessened the shaking. By history, four of the entire family who had tremor were considered to drink alcohol in excess. Also one of them without any tremor was regarded as a chronic alcoholic.

Apart from alcoholism, there was no history of psychosis or of subnormal mentality in this family. Those members who were questioned and examined appeared to be free of psychiatric disturbances. Their occupations were varied, but their industry was evident. Even those over 70 years of age frequently had gainful employment. Three with tremor had diabetes mellitus, and two others with tremor had noted premature graying of their hair. No history of these traits was elicited from other affected or nonaffected progeny.

There is a suggestion of longevity in this family. The ship captain of the first generation died at the age of 78. Two of his children survive at the ages of 88 and 91 years, the others having died at 65, 75, and 81 years. Of 10 subjects in the third generation, in one branch of the family, 4 are living over the age of 71 years. One died at 18, another at 46. The other six are alive but are less than 70 years of age.

While certain members of this family had large numbers of children, this fact does not seem significant, since there is a trend to large families in this region.

Neurologic examinations indicated wide variation in regard to the severity of tremor, even in siblings of approximately the same age. A tremor of the upper extremities was observed in 19 of the 24 persons examined. Shaking was evident in the outstretched fingers of the extended arm and hand. The tremor was slow (approximately four to six per second) and varied in amplitude and in frequency. In several instances the hand and forearm tremor was accompanied by gross movements of the upper arms. In an occasional subject, the tremor appeared to be more pronounced in the left upper extremity than in the right. This was not quantitated. With the hand at rest and supported, none had any visible hand or arm tremor. With the finger-to-nose test, it was observed that the tremor was maximal toward the end of a movement and persisted briefly after the finger had attained the nose. Little variation occurred when this test was performed with the eyes closed as compared with the eyes open. The head tremor, when present, always was of the negative type, the movement being horizontal, not vertical. The head movements seemed to be slightly slower in frequency and to be greater and more irregular in amplitude than the usual head tremor of Parkinsonism. No motion of the head was observed when the subject was recumbent. The facial tremor appeared to involve the buccinator muscles and the masseters. The voice defect was evinced as

Frequency of Tremor, by Generations, At Various Sites in Examined Subjects

Generation	Age Range, Yr.	Number Examined	Number with Tremor				
			Upper Extremities	Head	Face	Voice	Trunk
II	88	1	1	1	1	1	1
III	45-79	9	7	2	1	2	1
IV	34-50	8	7	4	1	1	0
V	12-28	6	4	0	0	0	0

a tremulous quality to the voice and never attained the characteristics of scanning speech. Two persons were observed to have intermittent slow trunk movements on assuming an erect posture. Tremor of the legs, tongue, and eyelids was not found. No subject had nystagmus, dysdiadokokinesis, cerebellar rebound phenomenon, or any gait disturbance. Normal associative movements were present with walking.

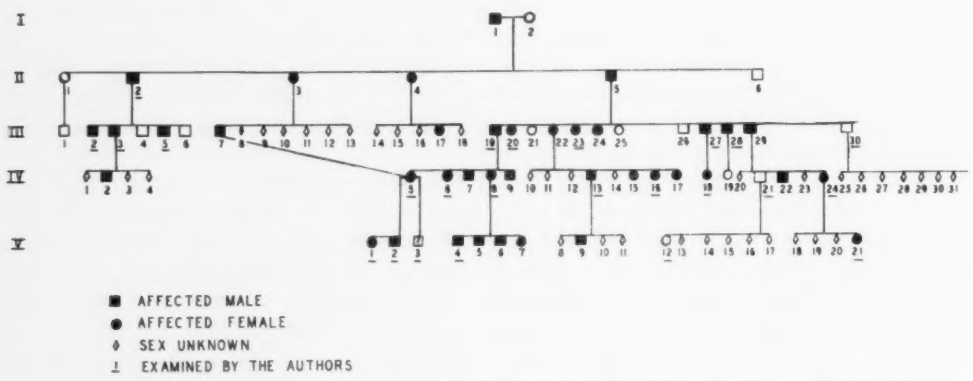
The handwriting of those with severe tremor showed the incoordination. However, those with less severe hand tremor frequently wrote well.

Observation of the affected subject while he was picking up scattered small glass beads proved to be a sensitive method for detection of this trait. The tremor was enhanced during this time; the movements were slow, deliberate, and awkward. Frequently beads were dropped in the process. This finding was present even in those with relatively mild tremor.

In the Table the frequency with which various regions of the body were affected with tremor is designated for the 24 subjects that were examined. For comparative purposes, this has been subdivided into generations. The most extensive involvement was present in the 88-year-old subject of the second generation (II-2) and in a 76-year-old man of the third generation (III-19) who had brothers and sisters of nearly the same age with less severe tremor (III-20, III-23). In the fourth generation, no apparent correlation between age and extent of tremor was observed. It is misleading to contrast the location of tremor of earlier generations with those of the fifth generation, who comprise a younger age group. It is probable that more extensive changes will appear in some of this generation as they become older.

The lack of reliability of the family histories of our subjects is interesting. Nineteen of 24 members of the family that were examined were found to have tremor of varying severity. However, on the basis of questioning numerous members of the family, only 4 of the 24 were thought to have this difficulty. Two others were presumed to have "shaking palsy."

The genetic chart for this family is presented in the Figure. The 24 who were ex-



Incidence of hereditary tremor in one family.

amined are separable from the other 58 persons in whom presence or absence of tremor was ascertained only by questioning multiple members of the family. Many of these live in distant regions of the country. No person was listed in the chart unless several members of the family at separate times gave identical information. Even here, there was disagreement about the number of children and their sexes. In several instances, the handwriting of a subject in a different area of the country provided evidence of the trait.

Definite signs of this disorder were noted when several children of affected persons were examined. Examination of a few children of noninvolved parents showed the children to be free of tremor. Similarly for the entire family, there was no example of transmission of the tremor by unaffected persons. However, additional studies are needed in this regard. One housewife (IV-5) had one normal or minimally affected child (V-3) by an unrelated and unaffected husband who subsequently died. This 28-year-old son had only a coarse tremor of the extended hands and lacked an intention tremor. Her second marriage was to a cousin of her father (III-7), a man who was reported to have the tremor. The two children of this union (V-2 and V-1) have severe tremors of their upper extremities at the ages of 12 and 14 years, respectively.

COMMENT

The pattern of tremor observed in this kindred fits well with descriptions of the disorder which has been termed benign essential tremor, hereditary tremor, familial tremor, or hereditary-familial tremor. Other observers * have commented on the different ages of onset of the tremor in affected persons and its variation in intensity among members of the same family. As in this study, the symptoms often appear in childhood or early adult life. Instances are recorded in which the condition was first observed as late as the sixth decade. This is difficult to evaluate, because the apparent late age of onset in a given instance may actually represent a period of aggravation of a mild tremor that was present but escaped notice in early adult life. This study partially confirms the observation that progression of tremor may ensue with advancing age, although this is not necessarily the case, as was noted here in some instances. The tremor commonly begins in the hands and may extend to affect the head, face, neck, tongue, larynx, diaphragm, lower extremities, and, rarely, the trunk. In the family described here, trunk involvement was noted twice, whereas leg tremor was not found. Many patients are aware that emotion aggravates their symptoms and that alcohol affords some relief. Exposure to cold, fatigue, and strenuous exertion may also enhance the tremor, although these stresses may also produce tremors in apparently normal persons.

In certain families, the tremor diathesis has been associated with other disturbances such as mental deficiency, psychosis, epilepsy, Parkinsonism, and frequently death from cerebral vascular accidents. Such defects may occur in members of the family that are affected or unaffected by tremor. The occurrence of chronic alcoholism in patients with hereditary tremor is frequent. It has been suggested the emotional instability predisposing to alcoholism may be inherited. It seems likely that the relief of tremor afforded by alcohol also may contribute to the development of alcoholism. The incidence of alcoholism in the kindred described here is relatively low. It perhaps is to be ascribed to chance that four with tremor and only one without tremor drank in excess.

The diagnosis of hereditary tremor may not always be easy. The familial history in conjunction with the presence of the static (antigravity) and intention tremor and in the absence of other neurologic changes usually permits a diagnosis. Difficulty arises in that one occasionally sees similarly distributed tremors in the absence of a familial history. Here it would be advisable to examine many other members of the family. The present study suggests that milder forms of tremor frequently are unrecognized. Basically

* References 1-5.

the symptomatology of hereditary tremor is that of a neocerebellar-like disorder. Many familial and nonfamilial diseases exist in which cerebellar symptoms are prominent.† However, disorders of gait and other neurologic abnormalities of a noncerebellar type may be present in such patients. In hereditary tremor, the gait and equilibrium are unimpaired.

Tremor per se should be regarded as a symptom. It may be encountered in anxiety, hyperthyroidism, general paresis, drug intoxications, and chronic alcoholism, as well as in disturbances of cerebellum and cerebellar tracts and in basal ganglia disorders.‡

The recognition of mild forms of hereditary tremor also is difficult. This may be illustrated by a subject (V-3) in this study. This 28-year-old man's only symptoms were those of a coarse hand tremor with excitement, exposure to cold, chronic fatigue, or mental strain (examination week in college); after taking small quantities of amphetamine, or following exertion such as heavy weight lifting. On examination, the extended fingers showed a slow coarse tremor (six per second). Other studies were negative. In this instance, re-examination after 10 to 20 years may provide a definitive answer.

The treatment of hereditary tremor is unsatisfactory. Reassurance as to its relative benignity is indicated. The erroneous diagnosis of Parkinsonism naturally causes great concern and should be avoided. It is likely that muscle coordination exercises will aid in some severe cases. Perhaps it is this involuntary training which made the tremor less marked in the right hand of the members of this family than in the left. There is little justification for the use of alcohol, although it is effective in reducing the tremor temporarily. Sedatives such as barbiturates, chloral hydrate, or paraldehyde seemed helpful in two severely affected members in this family. These drugs were compared with a placebo, which initially gave as good benefit but which ultimately was recognized by the patients as being ineffective.

There is much to be learned about the basic pathology of hereditary tremors. The anatomical study of Myle and Van Bogaert [3] demonstrated an abnormality in the cerebellum and pallidum in one case. In view of the frequency of hereditary tremor, it is unfortunate that so few pathological studies have been performed.

Several reports § consider the manner of inheritance of this trait. It has been suggested that there are several different modes of inheritance. Frequently the trait behaves as a non-sex-linked dominant. Instances are reported in which several generations appeared to escape tremor and yet it has reappeared in subsequent generations. Here one wonders whether actual examination of the members of the family might have revealed cases which had been overlooked.

In the present study, from the family history, 25 of 82 members of this kindred were thought to have hereditary tremor. Presumably this incidence is too low, since milder cases would escape recognition. However, it is also possible that some of the persons thought to be affected, by the history, may have had no involvement or may have had other disorders. On the basis of the family history coupled with examination of 24 members of the family, 15 additional subjects with the tremor were discovered. This makes the total number of affected persons to be 40 of 82, or an incidence of approximately 49%. This trait was detected in 19 of 24 persons that were examined. The exceptionally high incidence in this group likely results from unwitting selection. It would be necessary to examine a larger number of the family before the significance of this finding could be elucidated. However, the direct transmission of the trait through five generations and our failure to observe it among the offspring of unaffected persons strongly suggests that it is transmitted as a somatic dominant trait. An approximately equal occurrence was noted in the two sexes. It is of some interest that two affected members of this family married and produced

† References 5-9.

‡ References 5 and 10-13.

§ References 1 and 2.

two offspring who show the tremor in a distinct fashion at the ages of 12 and 14 years. It is possible that one or both of them carry the homozygous genes for hereditary tremor, which has resulted in the appearance of the well-developed trait at this early age. Observations on these two patients in future years may establish clinical differences as compared with the other, presumably heterozygous persons.

SUMMARY

In a single family with hereditary tremor, 24 members, extending over four generations, were examined for this trait.

In affected persons there was marked variation in intensity and distribution of the tremor.

Examination disclosed many instances of hereditary tremor which would have been overlooked on the basis of history taking.

In this family, the pattern of inheritance appears to be that of a simple somatic dominant.

Dr. Frank H. Tyler and Dr. M. M. Wintrobe gave useful criticism of this manuscript.

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Newer Concepts of Experimental Obesity

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An important aspect of obesity is its multiple causes. We are now on the threshold of understanding a few of these for the first time. Recent investigations have done much to unearth the evidence on the various factors.[1] The discovery of a fat-mobilizing or adipokinin activity in a relatively pure corticotropin preparation [2] opens other vistas. These studies leave the feeling that one is dealing with a new century of thought on this subject.

The concept that obesity is merely the result of overeating, or of an inflow of energy greater than outflow,[3] presupposes (1) that the obese has normal physiological responses and (2) that the person is a simple storage tank. Obesity now appears to be a qualitative physiologic change, metabolic and hereditary, in which the regulatory mechanisms of fat deposition * and conversion may be at fault.

A distinction, perhaps, should be made between obesity, a severe, often irreversible, disease, and simple overweight, reversible and based on a high ratio of caloric intake to activity or to rate of growth.

From the Endocrine Clinic, Stanford University Department of Medicine.

* References 4-6.

TABLE 1.—*Direct-Operating Factors in Obesity*

Factors	Probable Mechanisms	Probable Organ-System Involvement
1. Increased feeding (± relative inactivity)	1. Hyperphagia 2. Inability to recognize satiety 3. Other?	1. Hypothalamus 2. Cerebral cortex
2. Abnormal fat metabolism	1. Increased lipogenesis 2. Decreased mobilization of depot fat 3. Decreased rate of fat utilization and breakdown	1. Endocrine glands 2. Liver 3. Adipose tissue 4. Enzymatic systems

TABLE 2.—*Summary of the Possible Causes of Obesity*

Causes	Evidence
I. Intrinsic causes	
A. Constitutional	1. Yellow mice 2. Obob mice 3. Shetland Shepherd dogs 4. Identical twins 5. Human statistics
B. C.N.S.	
1. Hypothalamic 2. Cerebral	1. Hypothalamic lesions and stimulation 2. Prefrontal lobotomy
C. Endocrine	
1. Pancreatic	1. Obob mice 2. PZ insulin administration 3. Hyperinsulinism in humans
2. Pituitary	1. Adipokinin 2. Hypophysectomy + hypothalamic lesions
3. Adrenals	1. Adrenalectomy (survivors)
4. Adrenals and/or pituitary	1. Cushing's syndrome 2. Corticotropin or cortisone administration
5. Thyroid	1. Thyroidectomy + forced feeding 2. Propylthiouracil + forced feeding
6. Gonadopituitary	1. Yellow mice 2. Human menstrual disturbances, pregnancies, and obesity
D. Hepatic	
E. Enzymatic	1. Acetate block in obob mice
II. Extrinsic causes	
A. Abnormal food intake	
1. Quantity	1. Balance studies 2. Hypothalamic lesions
2. Quality (a) Unbalanced (b) Deficient (c) Toxic (d) Lipogenic	(Indirect and hypothetical)
B. Inactivity	1. Animal experiments
C. Trauma	
1. Toxic (a) Gold-thioglucose (b) Arsenic (c) Mercurials? (d) Tibione	1. Animal experiments 2. Clinical observation
2. Infectious 3. Surgical 4. Emotional	1. Clinical observation (sporadic)

The events leading to a disequilibrium of the weight regulatory mechanism may be divided into (1) the direct or operative factors and (2) the various possible causes of obesity. The operative factors (1) are listed in Table 1.

The various possible causes leading ultimately to obesity are listed in Table 2.

A. HUNGER AND RELATIVE FOOD INTAKE

The basic mechanisms which may account for phenomenal hunger have been proposed as (1) those due to afferent nerve impulses or to stimulation of the hunger center,[7] (2) hypoglycemia mediated by its effect on the stomach,[8] (3) high environmental temperatures,[9] and, most recently (4), the glucostatic mechanism suggested by Mayer and his associates.† The latter theory would explain the hyperphagia due to hyperglycemia as well as that due to hypoglycemia. It is based on a concept of "glucoreceptors" in the central nervous system sensitive to fluctuations of available blood glucose.

In the "glucostatic" view hunger would be integrated among the mechanisms through which the central nervous system insured its homeostasis.[1] Mayer and his associates found that temporary increases in blood glucose level normally correspond to decreases in food intake and vice versa. How could one then explain the hyperphagia in conditions with elevated absolute glucose levels, such as diabetes mellitus? The answer appeared to lie in the decreased tissue utilization of glucose ‡ in these instances. Specifically, there could be, in spite of a prevailing hyperglycemia, a decline in glucose available to the hypothalamic glucoreceptors, due to an impairment of phosphorylation. Evidence in support of this concept was derived by employing the peripheral arteriovenous difference, Δ-glucose, measured in the antecubital region, as an index of glucose utilization. Δ-Glucose was found to correlate closely with caloric intake and hunger feelings, regardless of blood glucose levels.§

A reduced capacity for taking up glucose has been demonstrated in the fatty tissues of obese diabetics by Törnblom and Hellman, employing continuous intravenous glucose-tolerance tests.[17] The arteriovenous glucose difference, the total glucose uptake, and the arteriovenous glucose difference-total glucose uptake ratio were found to decrease in the first 80 minutes in the obese as contrasted with normal controls. The decrease was most pronounced in those with a definitely diabetic oral glucose-tolerance curve.

The obesity experimentally induced by specific hypothalamic lesions offers evidence as to the role of hyperphagia,‖ and perhaps to the role of decreased mobilization of depot fat [25] as well. Hypothalamic obesity has been induced in the rat by bilateral lesions of the ventromedial nuclei, of the region dorsolateral to the mammillary bodies,¶ and of the tuber cinereum [20]; in the monkey by lesions in the suprachiasmatic and tuberal areas [21] and by damage to the ventromedial portion of the thalamus and rostral mesencephalic tegumentum,[22] and in the dog by lesions caudal to the paraventricular nuclei.[23] Stimulation of the lateral hypothalamic areas in unanesthesized cats by implanted electrodes also causes a pronounced increase in food intake, which returns to normal when stimulation ceases.[24] The size of the hypothalamic lesions, or of the stimulated areas, is important in determining what other associated metabolic effects (e. g. diabetes insipidus, gonadal changes) and what behavioral characteristics occur.

It appears that the weight gains of the hypothalamic obese animal may be divided into three phases [1]:

Phase	Characteristics
1. Postoperative	(*a*) Short-lived (*b*) Animal voracious
2. Active	(*a*) Intake excessive (*b*) Moderate but lasting hyperphagia
3. Static	(*a*) Weight stabilization (*b*) Hyperphagia slight or insignificant (*c*) Physical activity decreased

If fasting is undertaken in the static phase, there is weight loss with a resultant return to the active state. This cycle could possibly explain the recurrent weight gains in the human obese after repeated attempts at dieting. It has been suggested that the hypothalamic lesions actually might interfere seriously with the mechanism of stopping eating and somewhat less with the mechanism of hunger.[26]

† References 10-12.

‡ References 13-17.

§ References 1 and 10-12.

‖ References 18-24.

¶ References 18 and 19.

According to Kennedy, the overweight of the "hypothalamic" animals appears at first to be due to hyperphagia.[20] Later, after satiety, a cortical effect is observed: The animal eats a great deal only if the food is palatable. Once the obesity is established, the rat can maintain a weight about 50% above normal indefinitely without any significant increase in food intake. Kennedy found that old rats, tending toward weight gain, show the same reaction to palatability of diet as the animals operated on. He thinks that a circulating metabolite from foods or the fat depots is a stimulus to the hypothalamus. Further, he suggests that the obese human, like the older rat, has an inefficient hypothalamus.

An interesting case of hypothalamic-induced obesity in a human is reported by Heaney and associates.[27] Marked hyperphagia occurred suddenly during an aminopterin-induced remission in a 5-year old girl with acute lymphatic leukemia. The resulting obesity was confined chiefly to the face, trunk, and upper arms and was accompanied by generalized hirsutism. The 17-ketosteroid and 11-oxysteroid excretions were normal. There was no evidence of hypertension, glycosuria, or polyuria. Autopsy revealed a marked leukemic infiltration of the hypothalamus, and a subacute penetrating duodenal ulcer as well. This evidence of obesity due to definite pathology in the hypothalamus may shed some light on the obesity, sporadically reported,[28] in encephalitis and other infectious diseases as well as in brain injury.

Data on hypothalamic-induced obesity and the obesity following prefrontal lobotomy # lend support to the opinion widely held that in man emotional and psychosomatic factors may play an important part in this disease. Moreover, clinical observations on the sudden onset of obesity following severe psychological trauma have been reported.[30] Unfortunately, however, many of the studies on psychosomatic effects on obesity appear to have been undertaken without adequate controls.[1] Also, association of factors has been difficult to distinguish from actual causation; behavior patterns and obesity could be the result of a common constitutional lesion.

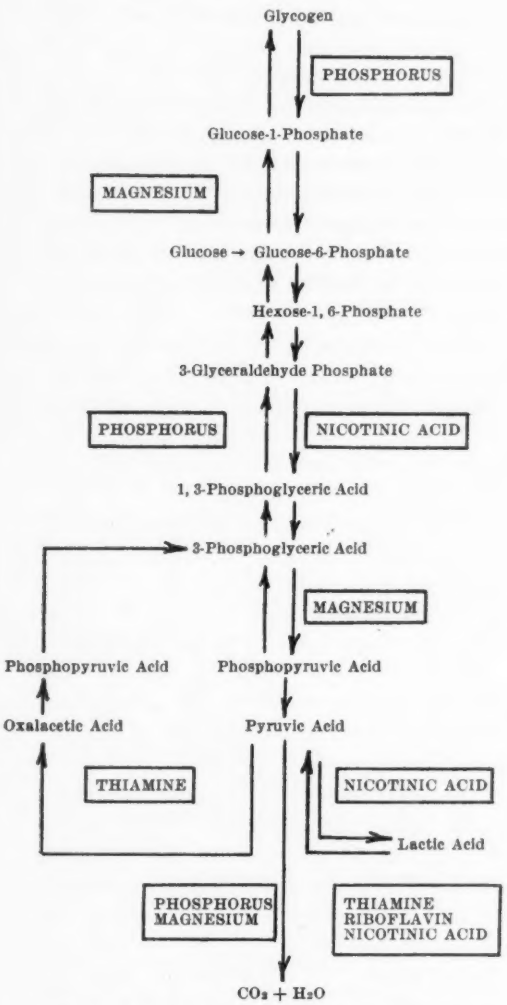
It has long been held that obesity in the human is based on high caloric intake alone, whether due to habit, hyperphagia, or emotional factors. This view is supported by an overwhelming amount of evidence in the form of balance studies. However, these studies give at most only a part picture of the problem. They would achieve a greater total significance if (1) types of obesity were better distinguished and (2) metabolic factors were eliminated. The tendency in the hyperphagic hyperthyroid person to lose, instead of gain, weight is an example indicating that the metabolic setting may be of prime importance in determining whether overeating will lead to obesity. Undereating, or deficiencies, of certain nutrients essential to carbohydrate and fat metabolism * might also be expected to contribute its effect (Figure).

Long suggests that the person who habitually overeats carbohydrates and other food in excess of needs deposits fatty acids in depot areas of the body, that the fatty acids formed from carbohydrates but not used require a certain amount of insulin over and above that needed by those who maintain a constant body weight, and that this insulin to all intents and purposes is wasted.[32] In other words, the continual and unnecessary addition of fat to the body stores may be regarded in its effect on the pancreas as an equivalent of partial pancreatectomy.[32]

Lack of physical activity may also contribute to the development of obesity. That exercise requires minimal caloric expenditure and is therefore of little concern is not borne out by tables on caloric requirements [33] and considerations of accumulated activity from day to day. In general, caloric intake follows energy expenditure.[1] Moreover, the

#References 1 and 29.

* Soskin, S., and Levine, R.: Carbohydrate Malnutrition, in Jolliffe,[31] Chap. 8, pp. 225 and 226; Williams, R. D., and Wilder, R. M.: Thiamine Malnutrition, in Jolliffe,[31] Chap. 18, p. 496.



Points of action of vitamins and minerals in carbohydrate metabolism. From Soskin, S., and Levine, R.: Carbohydrate Malnutrition, in Jolliffe, N., [31] New York, Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers).

influence of physical activity on weight gain has been demonstrated experimentally.† In obese-hyperglycemic mice which carry the waltzing gene and are in constant rotary movement, weight gains are only about 30% above those of the nonobese as compared with the 200% to 300% difference in the sedentary obese. The latter are 50 to 100 times less active than the nonobese. The decrease in activity antedates the obesity, and its energetic contribution is approximately double that of the excess food intake.[34]

† References 18 and 34.

B. TRAUMATIC FACTORS

While the expected role of food deficiencies and imbalance has not as yet been clearly demonstrated in the etiology of obesity, there is evidence that certain toxic substances can produce this disease. Gold thioglucose has been experimentally established as such an agent.[35] Arsenic in subtoxic amounts also appears to be capable of increasing fat deposition.[36] In humans, rapid weight gain has been reported with tibione (Conteben), administered to tuberculous patients.[37]

Obesity induced by gold thioglucose in mice was first described by Waxler and Brecher.[35] The mice appear to be healthy and active. They consume increased amounts when offered food and can mobilize their own fat in starvation. Morphologically they show only a centrolobular fatty infiltration of the liver. Owen and co-workers found no significant weight loss in the gold-thioglucose-injected mouse when on a diet diluted 50% with kaolin.[38] They suggested that this type of experimental obesity may result from serious interference with the satiety mechanism and less from interference with the hunger mechanism.

Besides toxic substances, other factors which may interfere with normal weight regulation, either by effects on the central nervous system and hypothlamus or through the endocrines, include traumatic events such as infectious disease, other existing pathology, emotional crisis, and perhaps even surgery.[28] In the case of infection and perhaps surgery, the concurrent events of enforced rest and excessive eating during such periods may explain in part the obesity which ensues. Any continued weight gains after these causes are no longer operative may be due either to the formation of new habits or, more likely, to metabolic or hypothalamic change. Engel states that, according to investigations not clearly understood, infection and injury are associated with alterations in

metabolism and that, further, the nature of these metabolic alterations is such as to put an increased demand on the pancreas.[39]

C. HEREDITY

Much evidence, experimental as well as statistical, has accumulated indicating that heredity plays a role in obesity. In 1927 Danforth demonstrated in a yellow strain of mice a hereditary tendency to become obese.[40] This tendency is carried by a dominant gene. The yellow gene in mice (A^y) causes obesity regardless of color combinations carried with it, even when the yellow color is suppressed, as in the albinos.[41]

The hereditary obese hyperglycemic syndrome in mice, carried by a recessive gene, was discovered in 1950 by Ingalls, Dickie, and Snell.[42] In these extremely obese mice, associated abnormalities occur,‡ such as atrophy and ulceration of the skin and endocrine changes, thus far mostly attributable to the pancreas.§ Fat is chiefly centrally located on the abdomen.[43] Caloric intake of the obese exceeds by 20% that of their nonobese littermates, while activity is 50 to 100 times less.[1] Inactivity precedes the obesity. The obese hyperglycemic mice are extremely sensitive to cold, and their basal metabolic rate, on the basis of body surface, is 40% to 50% less than that of their nonobese litter-mates.‖

A hereditary obesity based on a Mendelian recessive gene has also been noted in Shetland Shepherd dogs.[1] As with the obob mice, there is increased sensitivity to the diabetogenic action of growth hormone. Unlike the obob mice, the obese dogs show a preference for carbohydrates rather than for fats.¶ Evidence of hereditary obesity in humans is given in statistical studies of families and of identical twins having this characteristic.#

DIRECT FACTORS IN FAT METABOLISM

The possible sites of endocrine abnormality leading to obesity are the (1) hypophysis, (2) pancreas, (3) adrenals, (4) thyroid, and (5) gonads and may involve also the (1) liver, (2) adipose tissue, and (3) enzyme systems. The hormones [1] which have shown an effect on weight equilibrium are (1) insulin, (2) epinephrine, (3) growth hormone, (4) cortical hormone, and (5) thyroxine, and there is now new evidence also of important activity of (6) an "anti-insulin" hormone, or pancreatic hyperglycemic factor,[46] and (7) adipokinin.[2]

The various possible interactions of abnormal secretions from these sources alone are manifold and may explain in large measure the tendency of an individual person to remain thin or fat on his particular diet and with his degree of activity.

A hypothetical role of the pancreas has already been mentioned (1) by Long, who suggested that the continual addition of fat to the body stores might be regarded in its effect as an equivalent of partial pancreatectomy,[32] and (2) by Engel, who stated that infection and injury might put an increased strain on the beta cells of the islets of Langerhans which these cells cannot always meet.[39]

The importance of the pancreas in obesity might possibly have been predicted from the known association of this disorder with diabetes mellitus. An analysis of the weight of persons developing diabetes after the age of 40 showed that about 60% had been markedly overweight and an additional 25% had been moderately overweight; only 15% did not give a history of obesity preceding diabetes.[51] On the other hand, it has been demonstrated that insulin will accelerate the transformation of glucose to fat * and that experimentally prolonged use of protamine zinc insulin (unlike regular insulin [54]) will produce hyperphagia and obesity.† On the surface, the lipogenetic role of insulin would appear to be contrary to the observed frequent association of obesity and diabetes mellitus. However, these findings probably suggest that factors other than insulin depletion or insulin depletion alone may be in-

‡ References 1 and 43-46.
§ References 1 and 46.
‖ References 1 and 47.
¶ References 1 and 47.
# References 48-50.

* References 13-16, 52, and 53.
† References 55 and 56.

volved in this syndrome of diabetes and obesity.

One answer may be found in investigations on hereditarily obese hyperglycemic mice demonstrating the presence of a pancreatic "anti-insulin" hormone, as well as in those on the importance of the pancreas in a particular obesity.‡ In these obese hyperglycemic mice the only morphological endocrine change consists of hyperplasia of the islets of Langerhans; also, no lesions of the hypothalamus have been found.[47] An increased functional activity of the islets of Langerhans is indicated by their increased size and number, their rich capillary blood supply, the trabecular arrangement of the beta cells, and the striking beta cell degranulation.[46] The demonstration that in the obese hyperglycemic mice islets of Langerhans oversecrete a hormone with (1) hyperglycemic, (2) glycogenolytic, and (3) anti-insulin properties [46] suggests the possibility that this hormone plays a major role in the regulation of food intake and in the etiology of obesity.[46]

Evidence of the presence of such a hormone is derived from studies with diethyldithiocarbamate (DEDTC),[46] an agent earlier reported to damage the alpha cells of the pancreas.[57] Diethyldithiocarbamate was found to eliminate temporarily hyperglycemia, insulin resistance, and the response to growth hormone, characteristic of the obese hyperglycemic animals, and also to prevent the hyperglycemia normally following cobalt chloride injection,[46] At the same time DEDTC brought about the temporary restoration of beta granulation in these animals to levels comparable with those of the nonobese siblings. On the basis of these results it was concluded that obese obob mice may secrete in excessive amounts two pancreatic hormones, the insulin factor and a hyperglycemic "anti-insulin" factor, the trophic hormone to which is growth hormone. DEDTC treatment apparently elimnates temporarily the hypersecretion of the hyperglycemic factor, thus also the constant drain on insulin reserves. On the basis of previous evidence that DEDTC damages the alpha cells of the pancreas,[57] it would appear that the alpha cells are the most likely source of the "anti-insulin" hormone. There is also some evidence that somatotrophic hormone (S. T. H.) stimulates the pancreatic alpha cells to secrete hyperglycemic factor ("anti-insulin" hormone).[58]

The basic biochemical lesion of obesity appears to have been identified in the obese hyperglycemic strain as a partial block of acetate utilization with a resultant increased lipogenesis.[59] The question arises as to (1) whether the hypersecretion of a hyperglycemic factor in obob mice is an adaptive adjustment to the metabolic block to acetate oxidation or (2) whether an increased insulin secretion, responsible for the acetate block and increased lipogenesis, results from the tendency of the pancreas to correct for the primary hypersecretion of the hyperglycemic factor.[46] The finding of a greatly increased supply of insulin in the mature obese hyperglycemic mice tends to favor the latter view.

The endocrine involvement in the obese hyperglycemic mice is summarized from the various works of Mayer and co-workers § in Table 3 and includes findings which implicate the pancreas primarily and other glands perhaps secondarily.

Experimental evidence shows that organ involvement differs in the various forms of obesity. Compare, for example, the role of the pancreas in the gold-thioglucose-induced obesity or of the gonads in the yellow strain type with that of the obese hyperglycemic mice (Table 3). Thus, the gold-thioglucose-obese animals, unlike the obese obob mice, are sensitive to insulin and have a normal blood sugar level, which is unaffected by growth hormone.[60] Strain-mates of the obese hyperglycemic mice given gold-thioglucose develop the characteristics of the gold-thioglucose-obese mice, even though they are indistinguishable in appearance from their littermates who are hereditarily fat.

‡ References 1, 44, 46, and 47.

§ References 1, 46, and 47.

TABLE 3.—*Genetically Obese Hyperglycemic Mice (obob)*

I. Definite endocrine involvement

Gland	Abnormal Physiology	Source	Evidence of "Anti-Insulin" Hormone
Pancreas	1. Hyperglycemia 2. Increased insulin resistance	1. Hyperplasia of islet cells 2. Depleted beta granulations 3. "Anti-insulin" hormone	(a) DEDTC * (b) DEDTC + cobalt chloride (c) DEDTC + growth hormone (probable tropic factor)

II. Associated endocrine involvement?

Gland	In Favor	Against
A. Thyroid	1. BMR and oxygen consumption very low 2. Response to thyroid medication (a) BMR and oxygen consumption (b) Weight loss 3. Hypercholesteremia	1. No thyroid pathology 2. Insulin resistance 3. Thyroxine and TSH give little protection against the extreme sensitivity to cold 4. Radioactive iodine uptake and resistance to anoxia same as in nonobese 5. Thyroidectomy does not result in this syndrome in the nonobese
B. Hypophysis-Adrenal	1. Insulin resistance 2. Centripetal obesity 3. Cutaneous changes	1. Absence of pathology in these glands 2. Corticotropin or cortisone does not produce obesity in the nonobese siblings 3. Low liver glycogen 4. Extreme lability of blood glucose
C. Gonads	1. Refusal to mate	1. Normal gonads 2. Normal fertility

* Diethyldithiocarbamate.

Associated gonadal changes may also vary with the type of obesity. As contrasted with the obese obob mice (Table 3), the yellow strain shows more definite involvement of the gonads or gonad-pituitary axis: (1) Onset of obesity coincides with sexual maturity; (2) obese females show decreased fertility; (3) ovariectomy of the nonyellow females results in obesity.[40]

Associated gonadal changes have also been noted in certain obese human females.‖ Thus, 48% of patients with amenorrhea were found to be obese as contrasted with 13% in a control group.[61] Pelvic and systemic orders had been ruled out, and only patients 20% or more over ideal weight were classified as obese. Among 32 obese women with amenorrhea who were followed, it was found that a return of the menstrual cycle coincided with a decrease in body weight.[62] On the basis of these studies, Rogers and Mitchell suggest the possibility of a hypothalamic origin of both obesity and amenorrhea.[61]

Kossmann and Pirrung in a study of 24 obese women with adiposis of the trunk and of the extremities reported that pathological obesity became manifest in 10 after pregnancy ending in abortion or delivery and in 9 after menstrual disturbance.[63] One patient had a tumor of the pituitary, and another had been receiving tibione, a drug which has been reported to produce rapid weight gains in tuberculous patients.[37] Of the 9 women with menstrual disturbances, 8 showed definite atrophy of the sex organs, while among the 10 who developed obesity after abortion or delivery the hypophysis was thought to be involved.

Kossmann and Pirrung furnish laboratory evidence that obesity may be due primarily to diencephalohypophyseal dysregulation, at least in women between the second and fourth decades.[63] The increased incidence of obesity in the postwar period is explained on the basis of the functional unity of hypophysis and diencephalon and a diet deficient in protein.

In 1936 repeated injections of anterior pituitary extract were reported to cause increased transfer of fat to the liver, ketonuria, and decreased body fat.[64] New evidence now is provided that there is a definitive agent secreted by the hypophysis which has fat-mobilizing properties. Marked adipokinin activity, or fat-mobilizing properties, were demonstrated in oxidized cellulose, U. S. P. (Oxycel)-purified corticotropin in 1953 by Rosenberg.[2] Within three hours after injection in mice, doses of 3γ to 5γ produced an increase of 40% in the hepatic lipid concentration. Results supported the view that the

‖ References 61 and 62.

fat-mobilizing agent of the pituitary is probably a distinct principle.

The roles of the adrenal and thyroid glands probably vary with the form of obesity. In the obese hyperglycemic mice they appear to be secondary at best (Table 3). Evidence of more definite adrenal involvement in certain forms of obesity is evident from considerations of Cushing's disease as well as of corticotropin and cortisone effects.[39] Bomskov and Schneider found that adrenalectomized adult rats, which survived without supportive medication, gained in weight until generalized adiposity occurred.[65] Histologically, masses of hypertrophied adrenal cortex tissue, as well as thyroid atrophy, were noted.

Evidence of the importance of the intactness of the thyroid for normal weight equilibrium is indicated by experiments with thyroidectomy and propylthiouracil administration, either of which apparently facilitates the obesity brought on by forced feeding.[66] On the other hand, the majority of unclassified clinical obese patients appear to show no more evidence of thyroid disease than the nonobese. In 1947 Dr. George M. Curtis and I reported the whole blood iodine of 15 obese patients to be 4.1 ± 0.3γ/100 cc. (average ± standard error) as compared with 4.2 ± 0.2γ/100 cc. in 39 normal persons.[67] The basal metabolic rate was found to range from —19% to +24% (averaging ±0%) among the obese, as contrasted with a range of —19% to +21% (averaging —5%) in normal persons.¶ These differences are not significant. Lang reported the radioiodine uptake to be normal in 39 of 47 obese persons.[68]

Since the liver plays an essential role in carbohydrate metabolism and in fat mobilization, it may very well be expected to be another possible site leading to the abnormal metabolism of obesity. Thus far, liver involvement in the obese, when observed, has been that of fatty infiltration, an event interpreted generally as a result, rather than as a cause, of the obesity. Whether the fatty infiltration of the liver may further hasten the process of obesity or lead to its irreversibility requires investigation. The centrolobular fatty infiltration of the liver in gold-thioglucose obesity[35] could be the result either of the toxic agent or of obesity itself. If changes in the liver from gold-thioglucose induce the obesity, then we might expect more obesity due to hepatoxic agents.

The experimental obesity produced by hypothalamic lesions in various species appears to be accompanied uniformly by liver damage.[69] Zelman reports that in 20 obese human men, 50% to 100% overweight, all showed both laboratory and histological evidence (liver biopsy) of liver disease.[69] The sulfobromophthalein retention was abnormal in all; thymol turbidity and serum cholesterol were abnormal in half; urine urobilinogen was abnormally high in one-third; serum alkaline phosphatase was high in one-fourth; cephalin-cholesterol flocculation and cholesterol ester ratios were abnormal in one-fifth.

Some forms of obesity may be due to a metabolic defect involving adipose tissue itself. Adipose tissue is by no means inert. Experimental evidence indicates that it is actively involved in fat mobilization and in glycogen deposition followed by fatty acid synthesis.# Wertheimer and his associates have shown (1) that deposition and mobilization of fat in adipose tissue is an active process involving the metabolism of this tissue, (2) that synthesis of new fatty acids from carbohydrates as well as transformation of one fatty acid into another proceed continuously in this tissue, and (3) that all of these metabolic activities are regulated by nervous and endocrine factors.* Salcedo and Stetten reported that in obese mice given deuterium-fatty acid supplements the turnover of depot fatty acids is considerably slower than in the normal animals.[4] They concluded that the retardation of fat mobilization from the depots is an important factor in the pathology of obesity. In addition, Haagensen has interpreted the threefold in-

¶ Fertman, M. B., and Curtis, G. M.: The Relations of the Basal Metabolic Rate to the Blood Iodine in Nonthyroid Disease, unpublished data.

References 4-6, 70, and 71.

* References 5 and 6.

crease in phosphorylase activity of human subcutaneous adipose tissue as a manifestation of enzymatic adaptation.[71]

Pennington has suggested that many cases of obesity must be attributed to a defect involving the storage of body fat and that the impairment in the capacity of the enzyme systems for the oxidation of pyruvic acid may be a primary factor.[72] Guggenheim and Mayer have identified the basic biochemical lesion in the hereditary obese hyperglycemic syndrome as a partial block to acetate utilization.[59] That pyruvate and acetate can both give rise to active acetate (probably acetyl coenzyme A) is now reasonably certain.[73]

Pyruvate has been pictured as the "hub" toward which converge carbohydrate, fat, and protein in their catabolic and anabolic reactions.† At some point in carbohydrate metabolism, in the series of reactions below pyruvic acid, probably at the level of the two-carbon "acetyl-fragment," a fusion of pathways of carbohydrate and fatty acid metabolism may occur whereby the over-all conversion of glucose to fatty acid takes place, on the one hand, and the products of fatty acid degradation feed into the tricarboxylic acid cycle, on the other.[74]

Pennington cites the following evidence to confirm his thesis that pyruvic acid is a primary factor in the cause of obesity[72]:

1. Pyruvic acid is an intermediary substance in the conversion of carbohydrate to fat
2. It accumulates excessively in tissues of the obese
3. In certain concentrations it is able to
   - (*a*) check conversion of fatty acids to ketone in the liver
   - (*b*) check oxidation of fatty acids in the general tissues
   - (*c*) check oxidation of acetate
   - (*d*) stimulate formation of fat from smaller elements.

Deficiencies of nutrients essential to any single phase of normal carbohydrate and fat metabolism, including pyruvic acid formation and breakdown, should not be minimized in a consideration of obesity. In the Figure is made evident the role of certain known minerals and vitamins in these processes. Impairment of the enzyme systems involved may be due not only to nutritional deficiencies but also to heredity,[72] heavy-metal‡ and perhaps other intoxications, and certain metabolic disorders.§

That any step in fat metabolism may upset the weight mechanism is readily surmised. This may involve the higher centers or the endocrine glands or the various enzyme systems and may be a result of various interacting internal and external factors.

SUMMARY

A distinction should be made between obesity, a severe, often irreversible disease, and simple overweight, reversible and based on a high ratio of caloric intake to activity or to rate of growth.

Obesity takes many forms and is the end-result of various interacting factors, extrinsic and intrinsic.

The extrinsic causes of obesity include excessive caloric intake, and perhaps nutritional deficiencies as well; relative inactivity; toxic effects, and possibly stress situations. The extrinsic factors may bring certain of the intrinsic causes of obesity into operation.

The intrinsic causes include the constitutional, the diencephalohypothalamic, the endocrine metabolic, and the enzymatic. All of these may be iterrelated and interactive.

Anywhere along the pathways of the numerous intricate reactions of carbohydrate-fat metabolism, of fat mobilization, and of fat deposition, a disturbance might occur which conceivably could lead to obesity. There is now experimental evidence that in one known form of obesity the pancreas is involved. Although perhaps less conclusive, results indicate also that other endocrine glands, the adipose tissue, and enzyme systems play at least a part-role.

† Williams, R. D., and Wilder, R. M.: Thiamine Malnutrition, in Jolliffe, [31] Chap. 18, p. 496.

‡ Reference 72 and Williams, R. D., and Wilder, R. M.: Thiamine Malnutrition, in Jolliffe,[31] Chap. 18, p. 496.

§ Williams, R. D., and Wilder, R. M.: Thiamine Malnutrition, in Jolliffe,[31] Chap. 18, p. 496.

That hyperphagia or inability to recognize satiety may lead to obesity is demonstrated by experiments with hypothalamic induced lesions or stimulation. Again, metabolic factors may be concurrently involved.

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The Value of Tuberculin Testing

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Through the years, since its discovery, the tuberculin test has developed into a valuable means of discovering the trail of persons infected with tubercle bacilli. In spite of many studies of its value, many physicians still neglect the tuberculin test when the differential diagnosis of a pulmonary lesion is considered. The reasons for neglect of the tuberculin test appear to be manifold. First, there seems to be a feeling that "since nearly every adult is tuberculin-positive, there is little reason to do the test." Secondly, newer procedures in diagnosing lesions of the lungs are stressed, such as different positions of roentgenography, bronchoscopy, bronchography, cultures of tubercle bacilli, hemagglutination tests for tuberculosis, and laminography. The physician may become involved in the intricacies of the new tests rather than attempt to evaluate his patient on the basis of tried and true ones. Thirdly, the present-day treatment for tuberculosis has become so simplified, with such a low percentage of toxic or ill effects, that the temptation is very great to start treatment before clinching the diagnosis. Also, the trend toward ambulatory care of tuberculosis hastens the feeling that treatment should be started just as soon as a pulmonary lesion is found. Nevertheless, the physician must not forget that the diagnosis of tuberculosis carries with it great social, economic, and physical responsibilities. When a patient is branded as having tuberculosis, he immediately feels that he is a social outcast. Not only does he carry a certain amount of guilt over the possibility that he may have infected those with whom he has associated but the future bears a bleak possibility that he may break down and infect others around him. Also, he senses that to have tuberculosis labels him in society so that his friends will shun him lest they also catch his disease. The patient who is told he has tuberculosis is relegated to a long period of therapy, with hospitalization, drugs, collapse therapy, and surgery, all of which bear their mark upon his emotional makeup. The patient who must leave his family because of tuberculosis is no longer able to be the family breadwinner; when he is presumably well of his disease, he must assume a job which is not arduous and which undoubtedly will be less productive for him. For all these reasons and others peculiar to the individual patient, the physician who makes the diagnosis of pulmonary tuberculosis has a great responsibility. He must make the diagnosis with great certainty and caution. This presentation is made to show that the tuberculin test is a simple, cheap, and comparatively short test in which the possibility of a lesion being tuberculous can be ruled out; that it is one that has stood the test of time, and that it has not been supplemented by new and more intricate methods. It will become more valuable as our control of tuberculosis improves.

Read before the Southern Chapter of the American College of Chest Physicians, St. Louis, Mo., Nov. 6, 1954.

HISTORY

The material, tuberculin, was first discovered by Robert Koch in 1890. In experimenting with the material, he noted that if a normal guinea pig was inoculated with tubercle bacilli, the wound healed but reopened to form an ulcer in 10 to 14 days. Quite different was the result if a tubercu-

lous guinea pig was inoculated with tubercle bacilli. Here the wound closed, but in 24 to 48 hours the site became indurated, assumed a dark color, and finally sloughed to produce an ulcer. "The action of tubercle bacilli upon the skin of a normal guinea pig is thus entirely different from their action upon the skin of a tuberculous one. This effect is produced also by dead bacilli." [1] After working with the material, it was Koch's initial belief that he had discovered the cure for tuberculosis. However, subsequent use of tuberculin showed that this was not a cure for tuberculosis but only produced indurated nodules and ulcerations in persons into whom it was injected. It was at about this time that medical interest in the sensitivity of the skin to bacterial agents was stimulated. Pirquet noted that if he applied dead tubercle bacilli or their products to a scarified area of the skin, a modified reaction of the severe one as described by Koch would occur in a person who had tuberculosis. He studied a large number of children in Vienna, finding that there were 20% reactors in the 1- to 2-year-old age group as compared with 80% reactors in the 10- to 14-year-old group.[2] Hamburger, testing 532 children in the wards of a public hospital in Vienna, reported 9% reactors at 1 to 2 years to 94% reactors at 13 to 14 years. Looking back at these results one can see that the high percentage in young adults could be well explained by the fact that these were children from poor classes in slum districts, all of whom were seen in a sick condition. This did not reflect a complete cross section of the population. It was soon found that people did not have to have active pulmonary tuberculosis to have a positive reaction to tuberculin. Naegeli and Orth demonstrated that the majority of tuberculin-positive persons have healed tubercles within their bodies without having active tuberculosis. Thus, the concept was formulated that a person may have a well-encapsulated, healed, tuberculous lesion and still retain his skin sensitivity to tuberculin. By 1915 a certain amount of order had come out of the confusion concerning tuberculin testing. Veeder and Johnson published the results of tuberculin testing on 1321 children admitted to a hospital from the poor and more congested districts of St. Louis. They found reactors ranging from 24% at 1 to 2 years to 54% at 12 to 14 years. When those with clinical tuberculosis were excluded, the percentage of reactors in the 10- to 14-year-old age group was only 40%. Thus, we see that already the figure of 90% reactors as originally given by Pirquet had to be revised when a different type of population was considered. Thus, Slater, in 1924, found only 10% reactors to the tuberculin test in 1654 unselected school children, ages 6 to 16 years. This was in a relatively wealthy farming section in Minnesota. In 1948 he found only 1% to 3% reactors in a similar group. In 1935 Aronson surveyed the white population of six rural Michigan counties. Using first and second strength old tuberculin intradermally, he tested 8,025 persons, with the result of positives in 6% under 5 years, 18% at 10 to 14 years, and 76% at 40 years or over. Harrington and Myers, in a survey of children in Minneapolis, found that about 50% were reactors. Heatherington found that 75% were reactors in Philadelphia. Chadwick and Pope found half the number of positive reactors in 1939 that had been found in 1924 among Massachusetts school children.[3] Thus, one may say that the incidence of tuberculosis and positive tuberculin tests varies according to the individual's environment, economic status, contacts, and age groups. As tuberculosis control measures improve and less chance for infection exists, the tuberculin test will be less frequently found to be positive and thus will be of greater clinical significance.

Perhaps the best review of the literature and summary of available information concerning the tuberculin test was made in 1932 by Hart.[4] Working in a children's clinic and tuberculosis hospital in England, he made a comprehensive study of the various types of tests in use and came to certain conclusions about the reliability of the tuberculin test. He presented the evidence on which the conclusion is based that tuberculin hypersensi-

tiveness in human beings is the result of tuberculous infection.

1. Examination of the bodies of human subjects and cattle whose tuberculin reaction had converted to positive during life showed the presence of tuberculosis. He mentioned that Pirquet had examined 100 children and found that 30 out of 31 with positive tuberculin tests had gross evidence of tuberculosis, while 52 who had no evidence of tuberculosis were found to be tuberculin-negative. The Medical Research Council Tuberculin Committee of Great Britain, in 1928, had examined 114 cattle and found 37 of 39 positive reactors to have tuberculosis. Seventy-four cattle that were free of tuberculosis by examination were noted to be nonreactors to tuberculin. Kolmer, in 1923, reviewed the literature and found that in 15,000 instances there were only 2% to 3% of contradictions of evidence of tuberculosis and positive tuberculin skin testing.

2. The attack incidence (degrees of tuberculinization) shows that the degree of tuberculin positivity rises or falls with the evidence of tuberculosis found on necropsy examination.

3. The development of lesions of tuberculosis detectable by x-ray occurs simultaneously with the development of a positive tuberculin skin test. Also, the incidence of tuberculosis seen by x-ray rises in the same fashion and frequency as the degree of positive skin testing.

4. A positive tuberculin test in animals results when tuberculosis infection is induced.

Hart emphasized that there is no positive tuberculin test without a focus of tuberculosis under natural conditions. Although many laboratory experiments have thrown some doubt on the reliability of this, these are purely scientific curiosities and are of little clinical value. Occasionally a positive reaction to tuberculin can be obtained by injection of tremendous amounts of tuberculin, but this is a skin status that is not constant, and it is more a laboratory feat than a clinical fact. Occasionally people who are injected a second time with tuberculin will give a reaction when they did not the first time. Hart believes this to be due to the fact that the first test was really not negative but only so slightly positive as to be missed. The second contact with tuberculin increased the sensitivity to the point where a positive reaction could be obtained. Occasionally one finds instances in the literature in which tuberculosis could be proved in a person by culture or guinea pig inoculation when the tuberculin test was negative even to rather high concentrations. The number of instances in which this has been found is exceedingly small, and, as pointed out by Furcolow, the statistical frequency is so low as to emphasize the importance and reliability of the tuberculin test rather than to detract from its value.

METHODS AND MATERIALS

As has been mentioned, the first tuberculin test was a subcutaneous injection of tuberculin material by Koch. Since this produced a painful nodule that sometimes led to sloughing and ulceration, it soon had to be abandoned. In 1891 Epstein devised a test called the *Stichreaktion,* or needle-track reaction, which is a local reaction in the subcutaneous tissue. This was also found to be painful and difficult to interpret. Pirquet described a method in 1907 of superficially scratching the skin. This was simple and fairly easy to interpret, except that absorption of tuberculin material through the scratch was unreliable. In 1907 Calmette described the conjunctival method, but it was found to be too dangerous because of reactions of the cornea. Moro, in the same year, described an unction using tuberculin in a lanolin base. This was found to be harmless. The skin was abraded slightly, with light sandpaper, and the jelly was applied. In 1908 Mantoux described the intracutaneous method, which is the one used today. In 1932 Hart compared the unction with the intracutaneous method and found that the intracutaneous method was by far the most reliable. In 1937 Vollmer and Goldberger described the tuberculin patch test, wherein small squares of filter paper soaked in tuberculin were held in place against the skin by means of adhesive tape. The material was removed in 48 hours and read in 96 hours. This method was found to be about 85% to 90% accurate and carried the advantage of being less disturbing than injection by needle. However, opinion today is that absorption through the surfaces of the skin is irregular and not reliable. Thus,

the intracutaneous method, above all tests, is much to be preferred.

The tuberculin material has also gone through many changes since its original discovery. For many years the tuberculin material was called old tuberculin. This was simply the fluid medium in which tubercle bacilli had been grown, sterilized by heat, filtered to rid the material of debris and bacillary bodies, and concentrated by evaporation to one-tenth its original volume. However, different brands of old tuberculin were determined to be of different potency. Any manufacturing organization could put the material on the market, though its potency was not standard nor could it be relied upon. Different cultures of tubercle bacilli produced tuberculin varying in potency as much as 30 times. Seibert, in 1934, felt that a standard was necessary to insure sufficient strength as well as preventing overstrength.[5] She reported the isolation and preparation of a substance, later known as P. P. D., to serve as a standard for skin testing for tuberculosis. The material she finally obtained was a polypeptide of low molecular weight, probably about 2000 or less. The method was described as follows:

> The tubercle bacilli are grown on a standard, nonprotein, synthetic medium at 38 degrees for 6-8 weeks. The bacilli are killed by heating in a sterilizer. Glycerol and phenol are added; then ultrafiltration is carried out. To this solution 50% trichloracetic acid is added which precipitates the proteins and leaves the polysaccharides in solution. This precipitate is then dried and made into tablets.

In contrast to the old tuberculin, which was about 99% inert, this material was found to be extremely reliable and constantly potent. In the usual means of preparing the solution for use, the tablet is dissolved in 0.5 cc. of diluent and 0.1 cc. is injected intracutaneously. The injection should result in a small wheal on the surface of the skin. Otherwise, an injection which goes too deep may result in such a diffuse reaction that its interpretation will be difficult if not impossible. The "first strength" dose of P. P. D. contains 0.000,02 mg., and the "second strength," 0.005 mg. of the protein material. When either O.T. or P. P. D. is used, a positive reaction is one in which there is an area of induration produced at the site of injection in 48 hours. This area must be larger than 5 mm. to be considered positive. The test may be interpreted quantitatively as 1+ to 4+, though the significance of this is not agreed upon.

Mascher[6] has pointed out that there are instances in which a negative tuberculin reaction can be found despite the fact that a tuberculous infection undoubtedly must have occurred. He summarizes these conditions as follows: (1) after desensitization, (2) during the incubation period of the disease, (3) when the infection "has not taken" (for example B. C. G. vaccination or natural infection), (4) in cachexia, (5) in miliary spread of tuberculosis, (6) during the course of certain nontuberculous infectious diseases (transitory), (7) in "reversion" of previously tuberculin-positive, clinically healthy persons, (8) in biologically healed tuberculosis, (9) in old age, and (10) in certain cases of active tuberculosis. He presented a description of certain patients in whom he felt the diagnosis had been proved but in whom the tuberculin test remained negative. Six of these patients had disease from which the tubercle bacillus was cultured; two had acid-fast bacilli in their sputum but no tubercle bacillus was cultured, and three presented abnormalities believed to be tuberculous by roentgenographic appearance but in which bacteriological proof was not obtained. Furcolow,[7] in a discussion of Mascher's cases, pointed out that even if one does not question a diagnosis of tuberculosis in these patients the fact remains that only five persons in 1000 (0.5%) who had tuberculosis showed a negative tuberculin test. Also, in four years of sanatorium work only three cases of tuberculin-negative tuberculosis could be found. This would tend to indicate that tuberculin-negative tuberculosis is a rarity. Thus, for practical and clinical purposes the "tuberculin test would still be very useful and effective for the diagnosis of tuberculosis." Furcolow also pointed out that tuberculin in large doses may induce nonspecific reac-

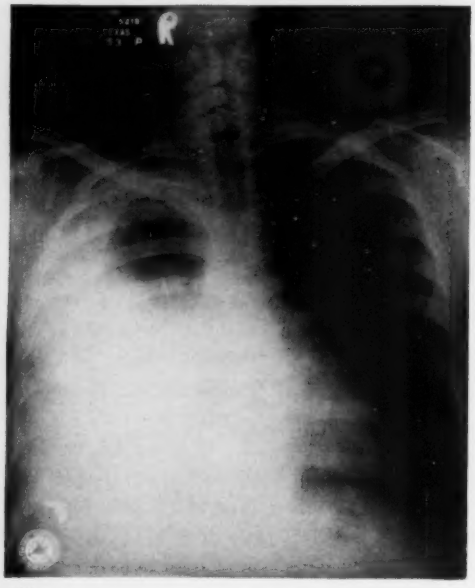
tions and that persons with tuberculosis are, in general, extremely hypersensitive to tuberculin. He stresses (1) that tuberculin is specific when employed in relatively low doses only and (2) that persons with tuberculosis, with very few exceptions, react to tuberculin.

The possibility that diseases of nontuberculous origin may produce tuberculin-positive skin tests has been considered. Dubois * has mentioned that there are two organisms, Mycobacterium ulcerans and Mycobacterium balnei, that cause illnesses, nontuberculous, that result in weak but definite tuberculin-positive skin tests.

In spite of these instances of tuberculin-negative tuberculosis and nontuberculous diseases which produce tuberculin-positive skin tests, for the practicing physician the tuberculin test is a very sound and extremely practical means of eliminating tuberculosis when a pulmonary lesion is presented for differential diagnosis. A negative reaction means that no tubercle bacilli are present, and a positive tuberculin reaction indicates the presence of a focus of living tubercle bacilli.

* Dubois, R.: Personal communication to the author.

Figure 1.



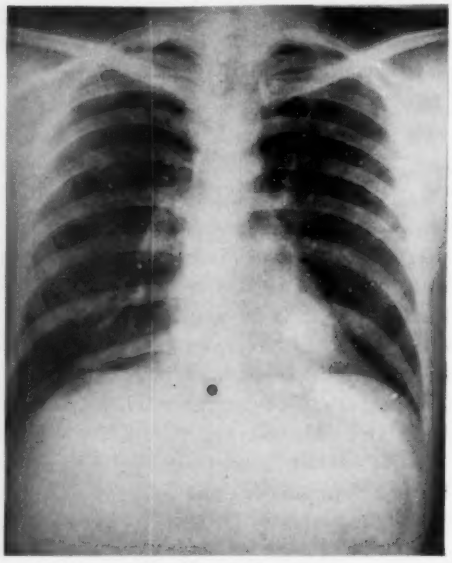


Figure 2.

REPORT OF CASES

The following case reports represent instances in which patients were considered to have tuberculosis or actually were treated for tuberculosis but the diagnosis was in error. The use of tuberculin tests would have eliminated the diagnosis of tuberculosis and directed the physician along different lines toward the true diagnosis.

CASE 1.—J. K., a 35-year-old white electrician, consulted his doctor in September, 1952, because of pain in the right chest, fever, and dyspnea. His x-ray showed a massive pleural effusion (Fig. 1). Without the benefits of skin testing or other diagnostic procedures, he was told that the effusion was tuberculous and was started on streptomycin and *p*-aminosalicylic acid. After three months of this therapy, during which time he did not improve, he was admitted to the V. A. Hospital, Houston, Texas. There the diagnosis of tuberculosis was strongly doubted. The tuberculin test was found to be negative in all dilutions. Exploratory thoracotomy was done, and a malignant lesion of the pleura was found. He was treated with intrapleural instillations of radioactive gold, and at this writing he is doing well.

Comment.—Although a pleural effusion accompanied by fever in a young man is usually thought of as tuberculous, in this instance the application of a tuberculin test would have ruled out tuberculosis immedi-

ately, and less time would have been lost in reaching a true diagnosis.

CASE 2.—G. P., a 35-year-old white student in a barber college, had never had any family history or personal history of tuberculosis; nor had he ever had any respiratory or thoracic complaints. In January, 1950, a mobile unit of the Houston Tuberculosis League x-rayed his chest, and he was advised to get a larger film. A 14 × 17 film showed soft mottled densities in both lungs (Fig. 2). In spite of the fact that he had no cough, sputum, hemoptysis, chest pain, weight loss, fever, sweats, hoarseness, or malaise, a diagnosis of tuberculosis was

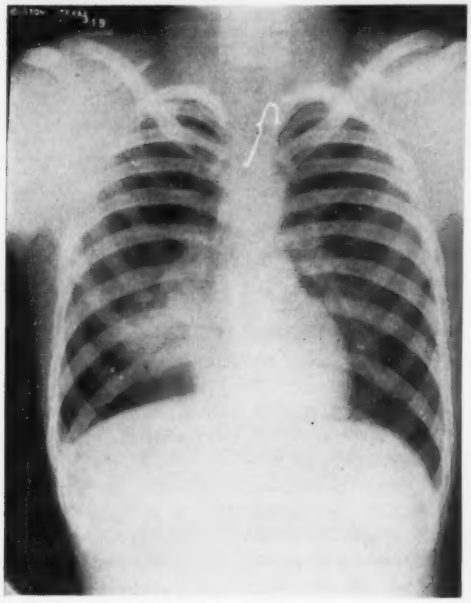


Figure 3.

made, and he was advised to quit work and await hospitalization. At the same time, three gastric cultures for tubercle bacilli were made. He was advised to stay away from his wife and child and not to work. When the first series of cultures were reported as negative for tubercle bacilli, further cultures were done. It was not until June, 1950, that skin tests of coccidioidin, histoplasmin, and tuberculin were done. All of these tests were negative, and the diagnosis of hematogenous tuberculosis was dropped. It was felt that sarcoidosis was the most likely diagnosis, and he was advised to have lymph node biopsy to confirm this. This recommendation was not followed through, and he was permitted to return to work at the barber college and to be with his family again.

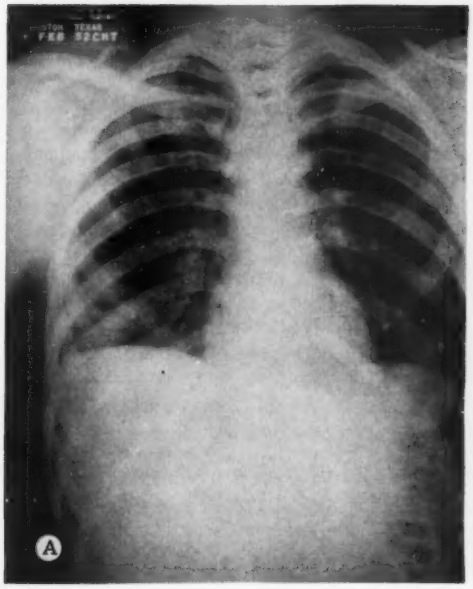
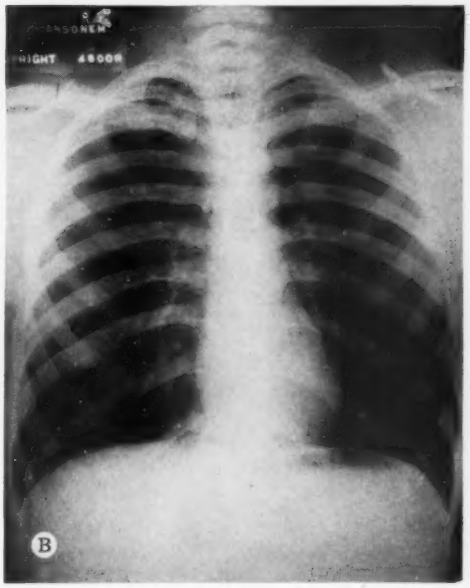


Figure 4*A*.

Comment.—Here the diagnosis of tuberculosis was again made without consideration of the clinical picture and was based primarily on roentgenographic appearance. A skin test would have ruled out tuberculosis immediately and prevented anxiety in the

Figure 4*B*.



patient, separation from his family, and time lost from school.

CASE 3.—W. S., a 14-year-old white student, was seen in November, 1953, because of cough, fever, pain in the right chest, sweats, yellow sputum, and weight loss. He had had a chronic cough and a history suggesting an allergic rhinitis. Because of the symptoms and the roentgenographic appearance of a density at the right base (Fig. 3), the patient was advised that he had tuberculosis and treatment should begin. Skin test to tuberculin in all dilutions was found to be negative. Further history revealed that two weeks previous to the time of the appearance of symptoms he had had a tonsillectomy with a fairly stormy postoperative course. In view of this history and the negative tuberculin test, it was felt that most likely he had an aspiration pneumonia. Treatment with erythromycin was instituted, with prompt alleviation of all symptoms and clinical recovery.

Comment.—Although a better history taken by this patient's physician would have turned suspicion toward the correct diagnosis, the use of the tuberculin test to rule out tuberculosis would have saved much anxiety on the part of the family and patient and directed the physician's thinking toward the proper diagnosis.

CASE 4.—H. W., a 25-year-old Negro asthmatic, was admitted to the hospital on the tuberculosis service on Feb. 29, 1952, because of chills, fever, malaise, and chest pain. An x-ray of his chest showed soft densities in both lungs, especially at the right base. Examination showed dullness at the right base and fever. Numerous crepitant rales were heard in both lungs. The x-ray strongly suggested tuberculosis (Fig. 4*A*), and numerous sputum samples and gastric aspirations were examined by concentrate and culture for tubercle bacilli. After eight weeks of hospitalization, these were reported as negative. During this time he spent in the hospital, he was on a tuberculosis ward where open tuberculosis was present. When the cultures were reported negative, skin tests were applied. His tuberculin test was negative on two occasions (P. P. D.). It was decided that his disease was not tuberculous but was probably a diffuse bilateral bronchopneumonia related to his asthma. He was treated with antibiotics and discharged on May 2, 1952, as well (Fig. 4*B*).

Figure 5.

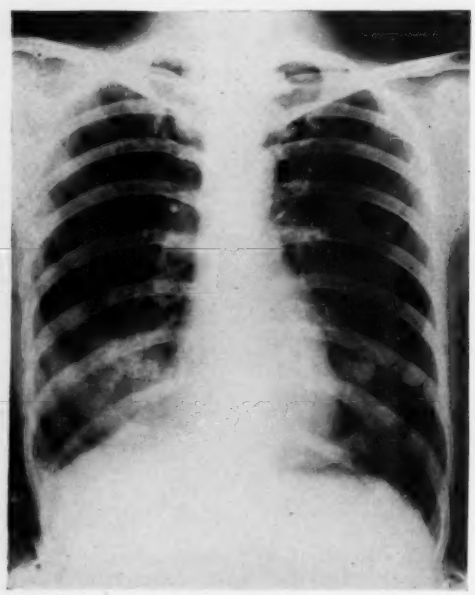
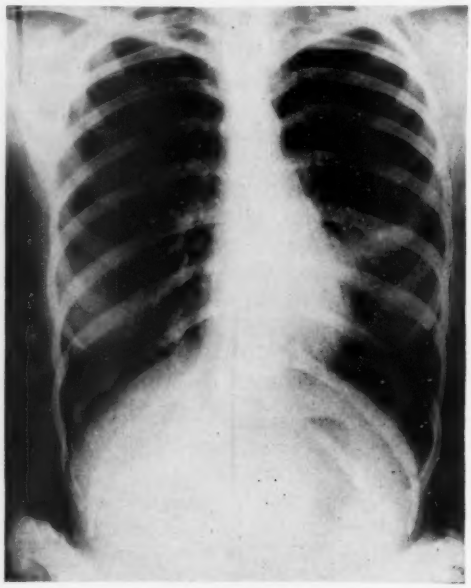


Figure 6.



Comment.—Although diffuse bilateral disease in a Negro strongly suggests the presence of tuberculosis, the routine use of skin tests would have pointed out the fact that tuberculosis was not present. This would have shortened his hospital stay and prevented his exposure to tuberculous patients in the hospital ward.

CASE 5.—J. Y., a 36-year-old housewife, coughed up about a teaspoonful of blood in May, 1953. An x-ray of her chest was taken, which showed a

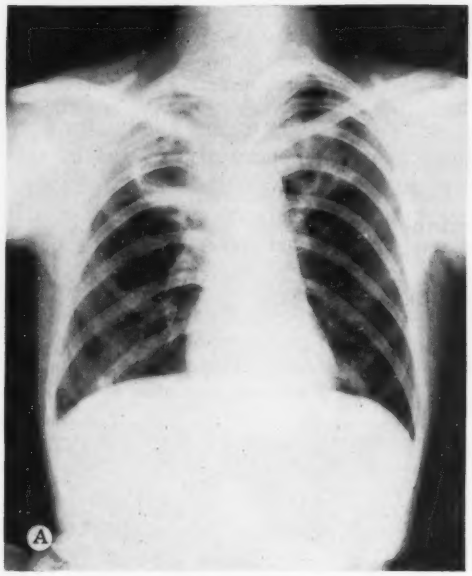


Figure 7*A*.

density at the right base (Fig. 5). This was interpreted by her radiologist as being tuberculous in origin. She appeared in my office, tearful and frantic at the diagnosis of tuberculosis and all of its implications. Skin tests with tuberculin, blastomycin, coccidioidin, and histoplasmin were applied and were negative. Bronchoscopy was negative, and bronchograms showed a small area of bronchiectasis in the right middle lobe. She was reassured that she did not have tuberculosis but that an area of bronchiectasis was the source of her trouble. She was examined one year later, and no change in her status was noted.

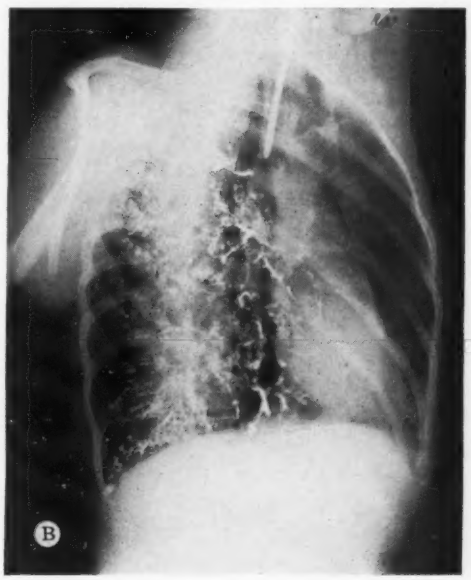
Comment.—The diagnosis of tuberculosis carried a tremendous emotional impact. Here a negative tuberculin test was used to reassure the patient that she did not have tuberculosis. Other diagnostic procedures and diagnoses then had to be considered.

CASE 6.—H. T. (Fig. 6), a 31-year-old office worker, consulted her physician because of anxiety and abdominal cramps in April, 1952. During x-ray examination of her gastrointestinal tract, fluoroscopy of her chest showed a density in the left midlung. Further questioning revealed that she had had a cough, weight loss, and anorexia of several weeks' duration. There was a family history of tuberculosis in that her paternal grandmother had had the disease. Because of the family history and present history suggesting pulmonary tuberculosis, she was referred for further care. Examination of her chest was negative except for fluoroscopy, which showed the density in her lung to lie anteriorly. Sputum examination was made, but she was advised that it would take six weeks to be certain that a culture would not produce tubercle bacilli. She was hospitalized. Skin tests for the fungi and tuberculosis were negative. Cold agglutinins were positive in a dilution of 1 : 448. It was believed that she had primary atypical pneumonia; she was treated symptomatically and recovered promptly. She was seen two years later, at which time examination of her chest was normal.

Comment.—Here an asymptomatic lung lesion was found and suspected of being tuberculous. The waiting period of six weeks to determine if a culture of her sputum would produce tubercle bacilli was obviously a long and agonizing one. A negative tuberculin test ruled out the possibility of tuberculosis, and primary atypical pneumonia was then considered.

CASE 7.—E. K., a 35-year-old housewife, was seen in a hospital emergency room because of chills, fever of 105 F, and right pleural pain. She had blood-tinged sputum and dyspnea. Bilateral cavities were noted on her chest film (Fig. 7*A*), and, with a diagnosis of far-advanced pulmonary tuberculosis, she was admitted to the Houston Tuberculosis Hospital on Jan. 22, 1952. She was bringing up large quantities of purulent material, but all cultures for fungi and tubercle bacilli were negative. Tuberculin

Figure 7*B*.



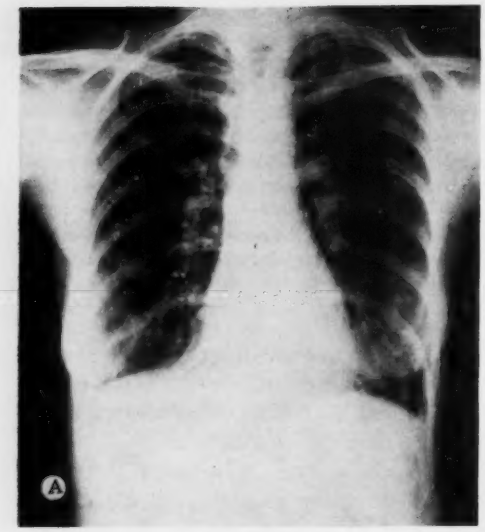


Figure 8*A*.

skin test on two occasions was negative, and complement-fixation and skin test for coccidioidin were negative. She was treated with penicillin; her symptoms resolved, and she was discharged improved on March 4, 1952. She was readmitted on May 14, 1954, because of hemoptysis, weight loss, and fever. She was producing 4 to 5 oz. (113 to 142 gm.) of purulent sputum daily. Repeat tuberculin (P. P. D. No. 2) test shortly after admission was again negative. She was treated with penicillin, became afebrile, and gained 25 lb. (11.25 kg.). Bronchograms were done on June 3 and 26, showing bronchiectasis in the right middle and right upper lobes (Fig. 7*B*). She was discharged from the hospital to continue her treatment away from a tuberculous institution in a general medical or chest clinic.

Figure 8*B*.

Comment.—Here the possibility of a nontuberculous pulmonary disease was considered on first admission. Because of the roentgenographic appearance of her disease, the diagnosis of tuberculosis was tenaciously held until bronchiectasis was proved by bronchogram.

Case 8.—M. T., a 43-year-old waitress, was admitted to the Houston Tuberculosis Hospital on Sept. 12, 1951. About one year prior to admission she had had an episode of fever, weakness, and cough. She was treated by a doctor with penicillin and improved slightly. In July, 1951, two months before admission, she again had a cold and lost weight. She lost her appetite. A chest x-ray was taken (Fig. 8*A*), and she was referred to the Tuberculosis Hospital. On admission, physical examination revealed restricted respirations bilaterally. Coarse post-tussive rales were heard over the left midchest posteriorly. Decreased breath sounds were present throughout. She had seven consecutive negative sputum examinations for tubercle bacilli on culture. X-ray on admission showed soft shadows in both lungs, with considerable clearing during her period of hospitalization. A bronchogram showed a saccular type of bronchiectasis involving all lobes of the right lung (Fig. 8*B* and *C*). Skin tests were finally done March 2, 1952, six months after ad-

Figure 8*C*.

mission, and O. T., 1:100, was negative. The final diagnosis of pulmonary fibrosis with bronchiectasis was made, and she was discharged on April 7, 1952.

Comment.—Here, again, the diagnosis of bronchiectasis was not suspected until purulent sputum failed to show the presence of tubercle bacilli on concentrate and culture. Only at this time were skin tests done, with complete elimination of tuberculosis from the differential diagnosis. Bronchograms revealed the true diagnosis.

CASE 9.—F. L., a 55-year-old single Mexican man, was admitted to the Jefferson Davis Hospital

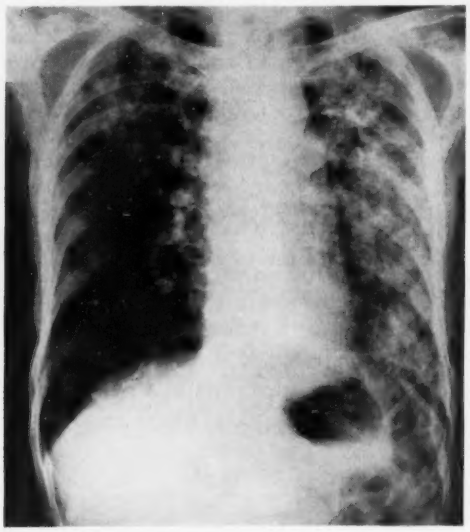


Figure 9.

emergency room in a cachectic condition and state of collapse on Oct. 23, 1953. An x-ray of his chest revealed what was thought to be far-advanced bilateral, active, pulmonary tuberculosis (Fig. 9). He was finally admitted to the hospital on Oct. 28, where treatment for tuberculosis in the form of streptomycin, *p*-aminosalicylic acid, and isoniazid was started. Physical examination revealed a cachectic person with a beefy red tongue, bronchial breathing, and dullness in the left lung and inspiratory and expiratory crepitant rales throughout both lungs. In addition to antituberculosis therapy, he was given sulfisoxacole (Gantrisin), penicillin, and oxytetracycline (Terramycin). On Dec. 28, 1953, he was transferred to the Houston Tuberculosis Hospital. He continued to improve there. Purulent sputum was cultured on nine occasions between Dec. 1953, and May, 1954, but all cultures were negative for

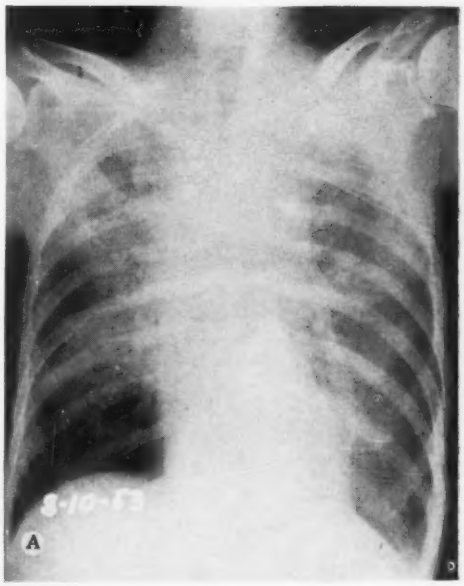


Figure 10*A*.

tubercle bacilli. Tuberculin testing was done on two occasions, on May 29, 1954, and again on June 24, 1954, both times fresh P. P. D., second strength, being used. Both of these tests were negative. The patient gained weight, felt better, and deserted the hospital July 21, 1954. It was believed that he had a bacterial pneumonia involving both lungs, and no evidence of tuberculosis was ever found.

Figure 10*B*.

Figure 11.

Comment.—Here the earlier use of tuberculin testing would have eliminated tuberculosis and prevented his occupying a much-needed bed in a tuberculosis hospital as well as preventing his exposure to tuberculosis. In addition, much waste of money in the use of drugs and nursing care for tuberculosis could have been eliminated.

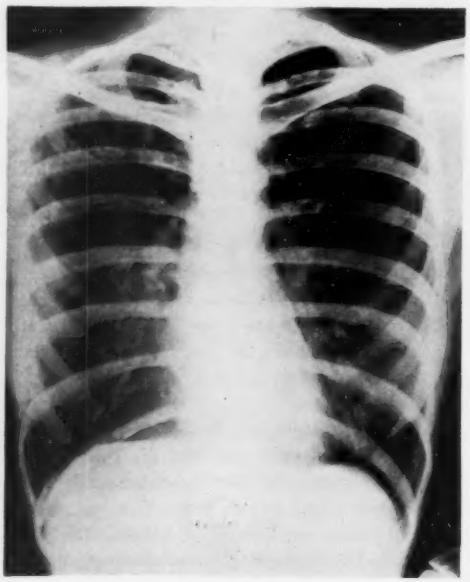
CASE 10.—E. P., a 66-year-old white man, was admitted to Jefferson Davis Hospital on June 9, 1953, in a confused and emaciated state. An x-ray of his chest had shown what was interpreted as pulmonary tuberculosis (Fig. 10*A*). Because of this, he was started on streptomycin and *p*-aminosalicylic acid. He showed marked clinical improvement but still required considerable care. He was transferred to the Houston Tuberculosis Hospital on Oct. 10, 1953. While in the hospital no positive smear or culture of his sputum for tubercle bacilli was obtained. On two occasions atypical acid-fast bacilli were found on smear, but these were negative on culture. Admission films to the hospital showed a large 4 cm. cavity with fluid level on the right. There was gradual closing of this with the continued use of antituberculous therapy as well as penicillin and sulfisoxazole. The patient was finally skin tested. On June 15, 1954, and June 24, 1954, his P. P. D. No. 2 test was found to be negative. It was felt that he did not have tuberculosis but had lung abscesses which had responded to medical therapy (Fig. 10*B*).

Comment.—Here, again, is a person who was treated for tuberculosis when no tuberculosis existed. Considerable time, money, and exposure to tuberculosis could have been saved if skin testing had been done to direct thinking toward a nontuberculous pulmonary disease.

CASE 11.—H. D. Jr., a 26-year-old sales manager, had never been out of Houston at any time in his life. He was first x-rayed in early 1950 and was told that he had had tuberculosis as a child and that he had scars on his lungs. In the latter part of 1950, another x-ray was taken and he was told that he had a touch of tuberculosis, with nicotine stains and measles scars on his lungs. In September, 1953, he developed cough and weight loss and was referred because of the possible diagnosis of tuberculosis. An x-ray showed numerous calcified densities in both lungs as well as densities in both hilar areas (Fig. 11). Skin tests were negative for tuberculosis but positive for histoplasmosis. It was felt that his weight loss and cough were due to an intercurrent respiratory infection, and he was treated with antibiotics, with excellent results. No evidence of tuberculosis was found, and he was reassured that he did not have and never had had tuberculosis.

Comment.—Here a patient could be reassured that he had never had tuberculosis and that the calcified densities in his lungs represented a healed form of a fungus infection with no threat to his future existence.

Figure 12.



CASE 12.—V. F., a 32-year-old clerk, had a long pulmonary history. At the age of 18 she had a cough and weight loss, and her doctor told her she had tuberculosis. No x-ray of her chest was made. She continued to have a chronic cough, and her weight was always poor. In 1947, she went to her family physician because of her cough, and an x-ray showed a density in the right upper lung. She was advised by a chest specialist that she did not have tuberculosis. In 1951 she had a severe attack of pleurisy and had to be taped. In June, 1952, a film by the Houston Anti-Tuberculosis League showed a suspicious area, and at the Houston Tuberculosis Clinic a large x-ray of her chest was made (Fig. 12). She was told that she had tuberculosis. She went to a chest specialist who fluoroscoped her, took her sputum, and four hours later told her that she had tuberculosis. She does not know whether tubercle bacilli were found or whether this was a clinical impression. In September, 1952, she was admitted to the Swedish National Hospital in Colorado. There seven sputum and seven gastric specimens were examined and found to be negative for tubercle bacilli by concentrate and culture. At this time the diagnosis of tuberculosis was put in doubt. Bronchoscopy and bronchography were done but were found to be normal. Following this, skin tests were done, and all were found to be negative except that for histoplasmosis. She was returned home in October, 1952. At that time skin tests were repeated, and the findings of the sanatorium were confirmed. Close examination of her x-rays showed that she had numerous emphysematous blebs in both lungs and that the density seen in the right upper lung probably represented an area of pulmonary fibrosis. Subsequent sputum samples have been examined for Histoplasma and tubercle bacilli, but all have been negative.

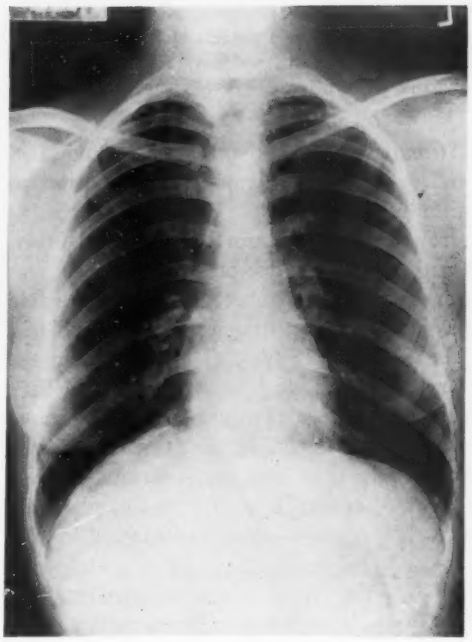
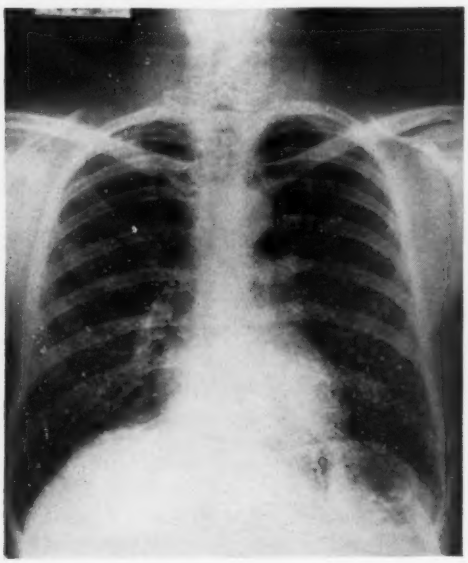


Figure 14.

Figure 13.



Comment.—In this case, the simple application of skin tests would have prevented the patient's being sent to a tuberculosis sanatorium and her having to give up her family, her job, and her friends and would have directed thinking toward the correct diagnosis.

CASE 13.—W. S., a 46-year-old white male laborer, had no family or contact history of tuberculosis. There is a history of a severe respiratory infection some time between 1920 and 1930. He was inducted into the army, but no chest x-ray was made. In November, 1941, he applied for an Army discharge because he was over age. An x-ray of his chest at that time showed numerous tiny calcified densities in both lungs (Fig. 13). No skin tests were made. Sputum studies were negative except that, out of 26 sputum cultures, 1 was found to be positive for tubercle bacilli. This was felt to be a laboratory error, and he was discharged from the Army with a record of service-connected healed miliary tuberculosis. Reexamination in May, 1951, showed the physical examination of the chest to be

normal. He had no symptoms and was working at arduous labor with no pulmonary complaints. Skin tests for tuberculosis, blastomycosis, and coccidioidomycosis were negative. A histoplasmin skin test was positive.

Comment.—Now that the concept of healed miliary calcification and its relationship to histoplasmosis is more widely known, this error should not again be made. However, even before the work on histoplasmosis was done, the use of a tuberculin skin test would have ruled out a diagnosis of tuberculosis. The fact that he was discharged from the service with a diagnosis of healed miliary tuberculosis also presents the added factors that future examinations for tuberculosis will have to be done and that compensation for tuberculosis may be given even though tuberculosis has never been present.

CASE 14.—F. W., a registered nurse, on an employment film at Methodist Hospital, Houston, Texas, was found to have numerous calcified densities in both lungs (Fig. 14). She was seen by a surgical resident who told her that "there was nothing wrong but that she should take it easy." With this advice ringing in her ears, she was not sure whether she was really sick or that she might ever become sick at any time in the future. Further history revealed that she was born in Arkansas and spent some time of her childhood in Memphis, Tenn. Skin tests for tuberculosis were negative, but those for histoplasmosis were positive. She was advised that she had not had tuberculosis and that her lung condition was completely benign.

Comment.—Here again, even if the concept of histoplasmosis was not realized, the simple use of the tuberculin test would have eliminated that possibility from this patient's mind.

SUMMARY

The diagnosis of tuberculosis must be made with caution and a sense of responsibility to the patient.

Historically, tuberculin has proved to be safe and reliable and to have a low percentage of error. For clinical use and practical purposes, the absence of a positive tuberculin test rules out the presence of tuberculosis.

Several case histories are presented to demonstrate the value of tuberculin testing in the consideration of pulmonary diseases.

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Pentaerythritol Tetranitrate in the Treatment of Angina Pectoris

Clinical Evaluation

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Although many drugs have been advocated for the treatment of angina pectoris, only the nitrites have proved unequivocally useful. Glyceryl trinitrate (nitroglycerin) promptly relieves the pain of angina pectoris, but its value as a prophylactic agent is limited by the short duration of its action. For this reason, various related compounds have been developed in an effort to find a long-acting drug which would prevent anginal pain.

Von Oettingen and his co-workers [1] studied the pharmacology and toxicity of pentaerythritol (Peritrate) tetranitrate in 1944. Subsequently, several favorable reports on its use in angina pectoris were published in Europe.* Winsor and Humphreys [4] studied the effect of pentaerythritol tetranitrate on 125 patients who had angina pectoris. They found that an average dose of 10 mg. three times daily produced satisfactory prevention of precordial pain in 78.4% of the patients. Glyceryl trinitrate requirement was reduced; exercise tolerance was increased, and the S-T segment depressions occurring after exercise were less marked. The results were superior to those obtained when the patients were give placebos, aminophylline, khellin, or a double salt of calcium theobromine and calcium salicylate (Theocalcin). Side-effects were infrequent and mild and consisted of headaches, nausea, and rash. Pentaerythritol tetranitrate produced no improvement in 96% of 125 patients who had chest pain of noncoronary origin.

Plotz [5] studied 35 patients with coronary artery disease, 15 of whom had mild angina; 15, moderately severe angina, and 5, status anginosus. Eleven of the 15 patients with mild angina were benefited; 13 of the 15 with more severe symptoms and all 5 with status anginosus noted good results. Despite the beneficial results obtained, no patient with moderate to severe angina was able completely to dispense with glyceryl trinitrate. Russek and co-workers [6] compared glyceryl trinitrate, papaverine, and pentaerythritol tetranitrate with other drugs in the treatment of angina pectoris. Glyceryl trinitrate was found to have a strikingly favorable effect both clinically and on the response to exercise as recorded electrocardiographically. Papaverine in a dosage of 1 to 2 grains (60 to 120 mg.) intravenously, or 3 to 8 grains (180 to 320 mg.) orally, was effective in some patients in decreasing or abolishing the abnormal electrocardiographic response to standard exercise. However, this effect was not obtained with the usual therapeutic doses of the drug. Of all the agents tested, pentaerythritol tetranitrate appeared to be the most effective drug for prolonged prophylacic therapy in angina pectoris. A 10 to 20 mg. dose afforded protection for four to five hours in the majority of patients, as judged by the electrocardiographic response to the two-step exercise test. The other drugs were essentially of no value.

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* References 2 and 3.

Weitzman [7] studied 65 patients who were divided into two matched groups; 34 received pentaerythritol tetranitrate, and 31 received placebos. The first group showed significantly greater benefit than the second. However, this advantage was not maintained when drug and placebo were interchanged.

Salans and co-workers [8] studied patients in whom they had previously evaluated various medications and in whom they felt the vagaries of angina were well characterized. They found that pentaerythritol tetranitrate produced no significant benefit. Talley and co-workers [9] studied 14 patients using placebo control methods and found that pentaerythritol tetranitrate in dosages of 30 mg. and 60 mg. daily did not reduce the number of attacks of angina when compared with a period of placebo administration. Riseman and co-workers [10] treated 15 patients with pentraerythritol tetranitrate in dosages of 50 mg. four times daily. Objective evidence of a favorable response, as determined by a standardized exercise-tolerance test, was obtained in only 3 of the 15 patients.

The current study was done to evaluate further the usefulness of pentaerythritol tetranitrate in the treatment of angina pectoris.

METHOD

Selection of Patients.—The criteria for selection of patients with angina pectoris for this study were similar to those used previously.[11] Many of the same patients were included. The patients were all men, living at the domiciliary of the Los Angeles Veterans Administration Center. Each patient was examined by several of the authors, and only those patients were selected in whom all concurred in the diagnosis of angina pectoris. Furthermore, the pain had to be of sufficient frequency and severity to allow evaluation of improvement. Twenty-three patients were selected, ranging in age from 55 to 80 years, with a median of 61 years. Four patients had previously had a myocardial infarction. Six patients had been in congestive heart failure, but all were well compensated at the time of the study. Eight patients had hypertension. Five patients had enlarged hearts. Eleven patients had normal resting electrocardiograms. These became abnormal in nine patients following single or double two-step exercise tests, and two patients were unable to perform the test because of orthopedic defects. The remaining 12 patients had abnormal resting electrocardiograms: myocardial ischemia and nonspecific S-T segment and T-wave changes were found in 6, left bundle branch block in 3, left ventricular hypertrophy in 2, and right bundle branch block in 1.

Technique of Procedure.—The double blind test suggested by Greiner and co-workers [12] was used throughout this study. Two of us (M. J. B. and L. R.) dispensed the medications once a week and issued the daily report cards without any comment to the patient. Each day the patients recorded the severity of the angina, employing the following terms: "no pain," "less than usual," "usual," or "more than usual." In addition, the patients recorded daily the number of anginal attacks experienced and the number of glyceryl trinitrate tablets used. Drug and placebo were interchanged at intervals unknown to the patients and to physicians G. M. K. and E. J. D. These physicians interviewed the patients once a week without seeing the daily report card. On the basis of the patients' statements they attempted to evaluate the degree of improvement and to decide whether the patient was receiving placebo or drug.

Each patient was first observed for a control period of six weeks without drug or placebo. The total period of study for most of the patients was approximately 40 weeks. Several patients were followed for 26 to 36 weeks, and one patient was followed for 20 weeks. In approximately half the patients placebo therapy initially preceded pentaerythritol tetranitrate, while in the other half the sequence was reversed. In general, each period on either drug or placebo lasted approximately six consecutive weeks. For the first month of therapy a dosage of 10 mg. of pentaerythritol tetranitrate three times a day was used; thereafter the doses of drug and placebo were doubled. The two-step exercise test was repeated at frequent intervals in nine patients in order to evaluate the effect of the medication on the electrocardiogram. These tests were done approximately one and one-half hours after the ingestion of either drug or placebo. The interpreters of the electrocardiograms did not know whether the patient was on placebo or drug at the time of the test.

RESULTS

The results of the study were evaluated in three ways: (1) interview evaluation, (2) analysis of the daily report cards, and (3) evaluation of the electrocardiographic changes following the two-step exercise test.

Interview Evaluation.—It was noted by both interviewers (G. M. K. and E. J. D.) fairly early in the course of the study that most of the patients felt subjectively im-

Effects of Pentaerythritol Tetranitrate and Placebo in Twenty-Three Patients with Angina Pectoris

	Av. No. of Days/Wk. in Which Cardiac Pain Was Described as				Glyceryl Trinitrate, Tablets/ Wk.	Anginal Attacks/ Wk.
	No Pain	Less Than Usual	Usual	More Than Usual		
Control period	1	1	4	1	15	21
Pentaerythritol tetranitrate, single dose *	1	2	3	1	11	15
Placebo, single dose	1	2	3	1	12	16
Pentaerythritol tetranitrate, double dose †	2	1	3	1	11	15
Placebo, double dose	2	1	3	1	10	13

* 10 mg. three times a day.
† 20 mg. three times a day.

proved. Despite the fact that the two interviewing physicians knew the medications were being changed, they were unable at any time to judge from the patients' statements when these changes occurred. A total of 634 patient-weeks were analyzed. Pentaerythritol tetranitrate and placebo were administered for 326 and 308 patient-weeks, respectively. The determination of which medication the patient was receiving was correct 63% of the time when the patient was receiving drug and 39% when he was receiving placebo. The highest proportion of correct evaluations for any patient was 65%. The total number of correct evaluations was 326 of 634, or 51%. The greater number of correct evaluations when the patients were receiving drug is a reflection of the fact that the majority of patients felt better most of the time. The proportion of patients who were considered improved was constant throughout the study.

Analysis of Daily Report Cards.—The Table presents the results of the report cards. It is noted that, in comparison with the control period, the patients improved slightly when receiving drug or placebo but there is no significant difference in improvement between the latter two. The data also fail to reveal any evidence that the order in which the medications were administered had any influence on the results. Although analysis of the results does not show any difference between the placebo and the drug, it was thought that, in determining averages, a real improvement in individual patients might be masked. For this reason, the results for each patient were carefully evaluated, with comparison of the data during the control period with the data while receiving placebo or drug. No patient showed any significant difference in his response to the drug and to the placebo.

Evaluation of Standardized Two-Step Exercise Electrocardiogram. — Nine patients were able to perform two-step exercise tests. These were done at intervals throughout the study, and the electrocardiograms were interpreted without knowledge of whether the patient was receiving placebo or drug. The final analysis was done by comparing the entire series of electrocardiograms for each patient and recording the degree of S-T segment depression and T-wave changes. It was found that there was a fairly marked fluctuation in the two-step exercise electrocardiogram from time to time for the same patient. However, there was no correlation between the degree of the electrocardiographic changes and whether the patient was receiving placebo or drug.

COMMENT

Evaluation of any medication by means of the patient's subjective response is extremely difficult. This is particularly true when the patient must compare intensity of pain with that experienced at some prior time. When the study is continued for a considerable length of time, the comparison of current pain with that experienced prior to the beginning of the study is probably valid only in the most general terms. The evaluation is slightly more accurate when frequency of specific attacks of pain and use of medication therefor are recorded. Unless the patient is conscientious about keeping his daily record, the data are likely to be erroneous.

The "double blind" method of Greiner and co-workers [12] appears to be the best method of evaluating a drug. Despite the drawbacks indicated, it tends to eliminate bias of the examining physicians and misinterpretation due to the psychological effect of the medication on the patient.

Pentaerythritol tetranitrate has been reported to decrease the S-T segment depression and T-wave changes in the two-step exercise electrocardiogram. In this study these beneficial effects were not confirmed. However, it was noted that there was a marked variation in the degree of the electrocardiographic changes after exercise from time to time. Russek [6] has emphasized the difficulty in evaluating results in such patients.

By all the methods of evaluation used in this study, no evidence could be obtained that pentaerythritol tetranitrate is of any benefit in the treatment of angina pectoris.

SUMMARY AND CONCLUSIONS

The effect of pentaerythritol tetranitrate on angina pectoris was studied in 23 patients by alternating placebo medication with the drug using the "double blind" method.

This study failed to demonstrate any beneficial effect of this drug on angina pectoris.

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Diabetes Insipidus and Pulmonary Fibrosis

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Diabetes insipidus has been found in association with xanthomatosis; sarcoidosis; pulmonary fibrosis; trauma; tumors; hemorrhage and infarcts; infections, including syphilis, tuberculosis, measles, mumps, scarlet fever, chicken pox, influenza, encephalitis, and actinomycosis; pellagra; hereditary and congenital lesions such as Laurence-Moon-Biedl-syndrome, pituitary dwarfism, and idiopathic diabetes insipidus.[1]

Many of the above conditions may cause or be found in association with pulmonary disease. The purpose of this paper is to discuss some of the relationships between the causes of diabetes insipidus and pulmonary disease and to present two cases of diabetes insipidus with pulmonary fibrosis and no known etiology.

CASE 1.—A 26-year-old white man was admitted to the National Naval Medical Center, Bethesda, Md., with an eight-month history of polydipsia and polyuria. He consumed up to 2 gallons (7.6 liters) of water daily and voided equally large quantities of urine. He voided approximately every 40 minutes and had nocturia as often as eight times each night. He had noted some fatigue and weight loss just prior to admission. His past history was negative except for the occurrence of pneumonia as a child. He denied any pulmonary symptoms or complaints. There was no evidence of occupational dust hazards.

Physical examination was essentially within normal limits. The initial routine chest x-ray (Fig. 1), on admission, revealed a diffuse nodular infiltration widely disseminated throughout both lung fields. The chest x-ray was compatible with hematogenous tuberculosis, or sarcoidosis, or pneumoconiosis, or histoplasmosis, or leukemic infiltration. Subsequently, the patient underwent extensive examination to determine the etiology of his diabetes insipidus and pulmonary findings.

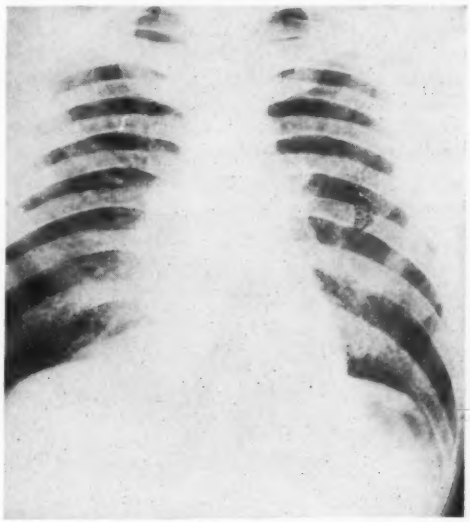

Fig. 1.—Chest x-ray reveals diffuse nodular infiltration widely disseminated throughout both lung fields, compatible with pulmonary fibrosis.

Skin tests with histoplasmin and coccidioidin were negative. The reaction to intermediate strength PPD was 2+. Complement-fixation tests for histoplasmosis, coccidioidosis, and blastomycosis were negative. Sputum examinations, bronchial washings obtained at bronchoscopy, and gastric washings were negative for tubercle bacilli both in culture and in guinea pig inoculations. On one occasion a species of Aspergillus was cultured from the bronchial secretions. This was believed to be a contaminant organism.

X-rays of the skull and hands were negative. An upper gastrointestinal series, barium enema, and intravenous pyelogram were negative.

Repeated urine analyses were normal except for low specific gravity, all ranging from 1.001 to 1.006. The specific gravity of 1.006 was obtained during a urine concentration test and was the upper limit of concentration. Laboratory examinations included normal liver-function studies and renal-function

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The opinions or assertions contained herein are the private ones of the writer, and are not to be construed as official or reflecting the view of the Navy Department of the or the Naval Service at large.

studies. The fasting blood sugar, glucose-tolerance test, blood urea nitrogen, PSP test, and spinal fluid studies were all normal.

The clinical course of the patient revealed a urinary output varying from 6,000 to 9,000 cc. per day. When he was given vasopressin (Pitressin) tannate, the patient's polyuria was easily controlled. During his stay in the hospital he was not bothered by any pulmonary symptoms. However, further pulmonary studies were completed in order to help establish the diagnosis. Pulmonary-function studies revealed 67% of normal for the calculated normal vital capacity and 75% of the calculated normal breathing capacity. Bronchoscopic examinations on two occasions were essentially normal.

Fig. 2.—Lung biopsy specimen of left lower lobe, which reveals areas of emphysema, fibrosis, and chronic inflammatory-cell infiltration. Diagnosis was chronic pneumonitis with pulmonary fibrosis.

A biopsy specimen (Fig. 2) from the left lower lobe of the lung was obtained, and microscopic study revealed areas of emphysema, fibrosis, and infiltration with chronic inflammatory cells. The pathological diagnosis was chronic pneumonitis with pulmonary fibrosis.

A chest film taken three years prior to admission to this hospital revealed marked pulmonary fibrosis. At that time, the symptoms of diabetes insipidus were not present.

The patient was relatively asymptomatic during his hospital stay. His diabetes insipidus was easily controlled by vasopressin tannate. He was subsequently discharged.

CASE 2.—A 21-year-old white man was admitted to the National Naval Medical Center, Bethesda, Md., with a three-month history of polyuria, polydipsia, anorexia, 10 lb. (4.5 kg.) weight loss, weakness, and nervousness. These symptoms began after an episode of mild upper respiratory tract infection. On further questioning the patient admitted to having had frequent colds and bouts of fever approximately nine months prior to admission.

Physical examination was essentially negative. However, the patient averaged 10,000 cc. of urinary output daily.

On admission, his chest x-ray showed a diffuse finely nodular infiltration of both lungs, which was interpreted as diffuse pulmonary fibrosis. An x-ray of the chest taken approximately two years prior to this examination was essentially negative. X-rays of the skull, hands and feet, and sacroiliac areas were essentially negative.

A skin test for coccidioidosis was negative. Skin tests for histoplasmosis were positive; however, complement-fixation tests were negative. PPD 1 and PPD 2 tests were negative. Numerous sputum collections, bronchial secretions, and gastric washings were negative for tuberculosis bacilli on culture and guinea pig inoculation. The vital capacity pulmonary function was within normal limits. A bone marrow examination was done and revealed erythroid hyperplasia and an increased eosinophilia. A culture of the bone marrow was negative for organisms.

The hemogram, blood urea nitrogen, fasting blood sugar, and liver-function studies were all within normal limits. A glucose-tolerance test, urinary 17-ketosteroids, and Robinson-Kepler-Power water-excretion tests were within normal limits.

An axillary lymph node biopsy specimen was normal histologically.

The urine analyses on several occasions were within normal limits except for the specific gravity, which ranged between 1.000 and 1.007 prior to treatment.

While in the hospital he was treated for an episode of acute upper respiratory infection with penicillin. The patient was given vasopressin tannate in oil, 2 cc. daily. The specific gravity of the urine while he was given this treatment ranged between 1.014 and 1.022. He did well subsequently and was discharged.

COMMENT

Diabetes insipidus associated with pulmonary disease has been reported by several authors. When the two conditions are found simultaneously, the commonest etiological factors are sarcoidosis, eosinophilic granuloma, or Schüller-Christian disease and, finally, idiopathic causes.

At least 11 cases of diabetes insipidus and pulmonary disease secondary to sarcoidosis have been reported.* The predilection of sarcoid involvement of the uveoparotid axis is well known. However, as reported in the literature above, the sarcoid granuloma may involve the hypothalamopituitary region more commonly than has been thought in the past. The pulmonary lesion of sarcoidosis is common, and those of heart, liver, and kidneys are well known.

Other hypothalamohypophyseal syndromes due to sarcoidosis have been observed at autopsy. The pathology and its location have been well described by several authors.†

Rowland, 1928, first described pulmonary fibrosis secondary to xanthomata granuloma.[17] His important work has led to the current concepts of eosinophilic granuloma of the lung and its pathogenesis.

Lichtenstein, 1953,[18] reviewed the subject of eosinophilic granuloma, Schüller-Christian syndrome, and Letterer-Siwe disease and integrated these entities as manifestations of the same disease. Other authors have also described such relationships.‡

Several cases of diabetes insipidus and pulmonary disease secondary to eosinophilic granuloma have been reported. Henschen, 1931,[21] in a monograph on Schüller-Christian syndrome, pointed out that pulmonary changes are the most important visceral xanthomatosis, since a diffuse pulmonary fibrosing lesion develops and may be the cause of death. It was pointed out that Schüller-Christian disease may occur in a variety of eight clinical forms. Three types may have diabetes insipidus and other visceral involvement. In this group lung involvement may or may not be present. The other five types may not have diabetes insipidus but have other visceral xanthomatosis, including that of the lung. Eosinophilic granuloma of the lungs, with or without bone involvement, and other types of visceral xanthomatosis have been reported.§

May, Garfinkle, and Dugan, 1954,[26] described three cases of eosinophilic granuloma of the lung. Their third case had an associated diabetes insipidus. Histologically, in the smallest pulmonary nodules the infiltration was of an interstitial nature, and eosinophiles or histiocytes were no more numerous than accompanying lymphocytes and neutrophiles. As the lesions became larger, there was thickening of the interstitial tissue, with encroachment on the air spaces. Emphysema developed, and eventually inflammatory cells and coalescence of diseased tissue formed granulomata with a ring of eosinophiles about the advanced lesion.

In the two cases presented here there were diabetes insipidus and pulmonary fibrosis with no apparent cause. It should be remembered that the relationship of diabetes insipidus and pulmonary fibrosis may well be a purely chance occurrence. However, one might postulate that these two conditions have a causal relationship but that the definitive pulmonary granuloma formation of perhaps sarcoidosis or eosinophilic granuloma has not had time to develop. It is interesting to note that in Case 2 there may well be a clue to the etiology, since there was an increased number of eosinophilic elements in the bone marrow. It is well known that this may occur in eosinophilic granuloma. With this in mind, one could project into the future that this case may develop into the eosinophilic granuloma type of process. Case 1 does not have such a clue.

The diabetes insipidus in both cases was easily controlled with vasopressin, and the frequent upper respiratory infections in the second case were controlled with antibiotics. Although there was marked pulmonary fibrosis in the first case, there were few respiratory symptoms. It is interesting to note the variation in time sequence and order in which the pulmonary changes in relation to diabetes insipidus occurred in the two cases presented. It is not known why this variation occurred.

In many cases cited in the literature pneumothorax occurred frequently and progres-

* References 2-11.
† References 12-16.
‡ References 19 and 20.
§ References 22-25.

sive right heart failure was the cause of death. Frequent upper respiratory tract infections were reported in some cases. Pneumonia occurred on three previous occasions in a case reported by Raffle, 1954.[27]

The x-ray findings in my two cases had the typical appearance of pulmonary fibrosis and what has been described as the "honeycomb appearance."

A number of cases of diabetes insipidus with so-called "honeycomb lungs" have been described.|| There is a great deal of confusion as to what "honeycomb lungs" represent. The term "honeycomb" roentgenologically may mean something entirely different than what has been described pathologically.

Cunningham and Parkinson, 1950,[34] described the histological features of "honeycomb lungs." They stated that this condition was characterized by thin-walled cysts, diffuse in distribution throughout both lung fields, with increased interstitial fibrosis. Most of their cases had no associated pituitary disorder. The term "honeycomb lungs" is a poor one and should be discarded. At best, it is only a descriptive roentgenologic term and may be associated with many diseases, including xanthomatosis, pulmonary fibrosis, granulomatosis, and tuberous sclerosis.

The pathological description of the lung biopsy specimen of Case 1 differs markedly from the pathological description of cases of so-called "honeycomb lungs," by Cunningham and Parkinson. It also is considerably different from the description by May and co-workers of eosinophilic granuloma of the lung. The striking pathological change was the presence of marked interstitial fibrosis with emphysema and marked inflammatory-cell infiltration indicative of an interstitial pneumonitis. A lung biopsy was not done in Case 2.

SUMMARY AND CONCLUSIONS

Two cases of diabetes insipidus associated with pulmonary fibrosis due to idiopathic cause are presented, with a review of the literature.

Diabetes insipidus and pulmonary disease may be found secondary to sarcoidosis, eosinophilic granuloma, and idiopathic causes. Other very rare etiologies have been claimed. A possibility of chance occurrence of diabetes insipidus and pulmonary fibrosis appearing together must be kept in mind.

The pathologic descriptions of the above pulmonary lesions are compared and contrasted.

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Skin-Test Reactions to Cat-Scratch Disease Among Veterinarians

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If one assumes that cat-scratch disease is an entity caused by a specific virus or other living or nonliving agent, the reservoir or source of this etiologic agent still remains unknown. The assumption that an infection has occurred may not be justified from the available findings, since this disease has been transmitted to only one human volunteer [1] and three or four monkeys * and has not been serially passed in any other animals or other media. Serological tests suggesting a relation of the disease to the psittacosis-lymphogranuloma virus group are also inconclusive. In addition, what were originally thought to be virus inclusion particles in epithelioid cells in lymph node granulomata of cat-scratch disease have been shown to be particles present in many other viral and nonviral granulomatous diseases.[2] However, in order to start an investigation of this disease one might well assume the existence of an etiologic agent and try to define it and/or its habitat further.

The most obvious fact related to the possible source of etiologic agent is the frequency of cat contact of those with cat-scratch disease. In the largest review of cases [3] yet published, the incidence of cat contact was 83%, while that of cat scratch was 54%. The largest collection of cases in the United States [4] gave the incidence of cat contact as 92% and that of cat scratch as 58%. Yet it has been known almost from the beginning that other dermal inoculations without known cat contact may produce the disease.[5] In addition, the cats thought to be involved in the disease transmission are uniformly well and skin-test-negative. Early in the history of the disease the idea arose that the cats, if involved, must act as passive carriers. Those [6] who tend to minimize or reject the role played by the cat use the term benign inoculation lymphoreticulosis instead of cat-scratch disease. However, incidence of cat contact mentioned above, plus other pieces of evidence such as small family epidemics occurring only where a family cat is present,[3] strongly suggests that the cat in some way is most often involved in this disease. Interesting is the fact that the only endemic area yet recorded is a town in France where the French National Veterinary College is located.

Those who have considered the role of the cat as significant have postulated that a reservoir of etiologic agent might likely exist in the natural prey of cats, such as birds or mice. Studies along this line have shown no similar disease to exist in birds or rodents,[3] but the inability to isolate an etiologic agent, plus the great difficulty, if not insurmountable task, of producing the disease experimentally, has rendered any investigation of material from cat claws, fur, saliva, etc., or from birds or mice inadequate. For a while it was suggested that feline pneumonitis of Baker, caused by a member of the psittacosis-lymphogranuloma virus group, might be responsible. In order to test this idea, lymph node material from human cases of cat-scratch disease was inoculated intranasally into mice, and this produced no significant

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* Reference 1 and Gifford, H.: Unpublished data.

mouse pneumonitis.† This, coupled with the facts that the involved cats are skin-test negative to cat-scratch disease and have no history of recent feline pneumonitis, makes the role of feline pneumonitis unlikely.

It occurred to me that the one group having the most contact with both sick and well cats, and with all possible animal reservoirs for an etiologic agent, was that of the practicing veterinarians. Hence it was decided to survey a group of veterinary physicians in the localities from which I had received several active cases of cat-scratch disease. The two areas chosen were San Francisco and Petaluma, Calif. In all, 28 veterinarians were included. Each was questioned about his background in the field of veterinary medicine and his type and frequency of skin inoculation while handling animals. Each was skin-tested with a cat-scratch disease skin-test antigen made from pus aspirated from the epitrochlear lymph node of one patient. This patient gave a history compatible with cat scratch disease [7] and was skin-test-positive to antigen supplied by Daniels and MacMurray and to his own processed lymph node pus. This antigen has been used on 84 cases of clinically suspected cat-scratch disease, giving 33 positive reactions and 51 negative reactions. Included in the negative group were cases of tuberculosis and suppurative bacterial adenitis, as well as nonspecific lymphadenitis and reactive lymph nodes in systemic diseases. The skin-test material was therefore considered to produce specific reactions for cat-scratch disease. Complement-fixation tests were run on serum from a few of the veterinarians with antigens of the psittacosis-lymphogranuloma virus group, brucellosis, and Q-fever.

The findings were as follows: Seven of the 28 veterinarians gave well-defined positive skin tests with erythema and induration. Five reacted within 48 hours, and one, in 72 hours, while one had a late reaction, occurring seven days after the inoculation. This late type of reaction is occasionally seen in patients with active cat-scratch disease. The positive group was compared with the negative group in as many ways as seemed pertinent. This is summarized in the Table. There seemed to be no statistically significant differences between the two groups.

The veterinarians were questioned about all types of inoculating skin trauma. The frequency of cat scratches was quite prominent in both negative and positive groups. Bites were much less frequent. The only other type of frequent skin trauma occurred from dogs. Bites were commoner than from cats, but scratches still predominated over bites. Other inoculating skin trauma occurring once or occasionally in one or more members of the positive group were produced by skunk, chinchilla, rabbit, fox, and birds. One or more members of the negative group also had suffered skin wounds at some time from chinchilla, rabbits, fox, birds, hamster, rats, monkey, guinea pig, mink, and ferrets. The negative group thus had a wider range of inoculating skin trauma by animals.

Data from Twenty-Eight Veterinarians Skin-Tested for Cat-Scratch Disease

	Veterinarians Skin Test	
	Positive 7	Negative 21
1. Frequency of cat scratches and bites		
1/wk. or more	4	6
1/mo. or more	6	17
2. Frequency of dog scratches and bites		
1/wk. or more	3	4
1/mo. or more	4	11
3. Average age, yr.	48.8	40.2
4. Range of ages, yr.	29-68	21-71
5. Average yr. of large-animal practice	8.6	3.3
6. Range of yr. of large-animal practice	0-25	0-25
7. Average yr. of small-animal practice	16.3	10.7
8. Range of yr. of small-animal practice	5-32	0.5-28
9. Number having done large-animal practice	6	11
10. Other types of practice		
Meat inspection	2	6
Poultry	0	3
11. Previous disease transmitted by animals	2	2
12. Previous lymphadenopathy	5	6

The average age of the positive group was greater than that of the negative group, but the difference was not statistically significant when tested by Wilcoxon's two-sample test.[8] The age range was practically the same

† Gifford, H.: Unpublished data.

in both groups. The average years of large-animal practice was considerably greater in the positive group, but, again, the difference was not statistically significant when tested by Wilcoxon's two-sample test, and, again, the range of years of practice was the same in both groups. Six out of 7, or 86%, of the positive group had done large-animal practice, while 11 out of 21, or 54%, of the negative group had handled large-animal practice at one time. The average years of small-animal practice was greater in the positive group also, but still the difference was not statistically significant, and the range of years was about the same in each group. The other types of veterinary practice included meat inspection, done at one time by two of the positive group and six of the negative group, and exclusive handling of poultry, done one time by none of the positive and three of the negative group.

Most of the veterinarians tested were at the present time doing a small-animal practice. All had had a relative common background of animal contact in veterinary school, although their practices over the years had been diversified. Only two veterinarians in each group had suffered from any disease known to be transmitted from animals to man. Two of the positive group and one of the negative group had had brucellosis. One of the negative group had had tularemia.

Previous lymphadenopathy of sufficient degree to be recognized and remembered occurred in five of the positive group and six of the negative group. Two of the instances of lymphadenopathy in the negative group were not explainable on the basis of other local or systemic diseases. They might possibly have been clinically compatible with cat-scratch disease. Not enough could be recalled of the instances to define the attacks further. Two of the positive group similarly had histories of lymphadenopathy without local or systemic diseases to account for them. In one no cat scratches or other inoculation trauma could be recalled. In the other there was a large inflamed cat scratch and swollen tender epitrochlear lymph node present at the time of the skin test. The physical examination and subsequent clinical course of this veterinarian was typical of cat-scratch disease. In general, however, there was nothing to indicate that the other veterinarians in either the positive or negative group had had a definite clinical episode of cat-scratch disease. In fact, as has been mentioned elsewhere,[9] the disease was practically unknown to the veterinarians.

It was possible to obtain serum from four of the positive group, and complement-fixation tests were made for psittacosis, lymphogranuloma venereum, feline pneumonitis of Baker, Q-fever, and brucellosis. Three of the four veterinarians were negative to these complement-fixation tests, while the fourth, described as Case 3 below, showed titers of psittacosis 1:4+ and lymphogranuloma venereum 1:2 ±, which were not considered significant. Similar complement-fixation tests were made on serum from five of the negative group. The results were interesting but not otherwise helpful. One of these was negative; a second showed 1:8 + titer against Brucella; a third showed psittacosis 1:8++++, feline pneumonitis of Baker 1:8++++, and lymphogranuloma venereum 1:4+++; a fourth showed 1:2 ++++ titers against psittacosis, lymphogranuloma venereum, and feline pneumonitis of Baker, and a fifth showed psittacosis 1:32++++, lymphogranuloma venereum 1:16++++, feline pneumonitis of Baker 1:16++++, and Q-fever 1:2+++. There seemed to be more response, although significant in only one instance, to the psittacosis-LGV group among the members of the negative group tested.

Originally it had been planned to survey a larger group of veterinarians, but the study was brought to an abrupt halt by severe and persisting reactions which occurred in the positive group. These were found in four of the seven positive reactions. Briefly, they were as follows:

CASE 1.—N. F. had an area of erythema of 1.5 cm. diameter and an area of induration of 1 cm.,

48 hours after skin-test inoculation. This grew to an area of erythema of 4 cm. over the next few weeks, with an indefinite margin of induration. It ulcerated centrally for five months, healing sporadically and then breaking down again. At the end of 10 months there remained an area of 1.5 cm. diameter of dusky red erythema with a 6 mm. plaque of indurated tissue suggesting scar.

CASE 2.—C. B. M. had an area of erythema 1.8 cm. in diameter and an area of induration of 1.3 cm. within 48 hours. These did not extend, but, instead, a nodule of 0.5 cm. elevation and 1.2 cm. diameter gradually developed. This had a narrow, roughly 0.2 to 0.3 cm., dusky-red margin of erythema and was itself dusky-red and mottled with yellow areas of underlying necrosis. The latter areas sporadically broke down, to discharge a little necrotic material. Ten months after the skin-test inoculation the nodule was still the same but was reduced in size to about 0.9 cm. and 0.3 to 0.4 cm. elevation.

Fig. 1 (Case 3, B. T.).—Site of skin test eight months after inoculation of skin-test antigen, immediately before lesion was removed surgically.

CASE 3.—B. T. had no reaction within 48 hours but showed an area of erythema and induration of 1 cm. diameter within 72 hours. Over the next few days the erythema extended to 1.5 cm., while the induration remained unchanged. Gradually, over the next few months the area of erythema paled and lessened in diameter to about 1.2 cm., while the indurated area persisted as a central paler region of 0.8 cm. and lasted until the lesion was surgically removed after eight months' duration (Fig. 1.)

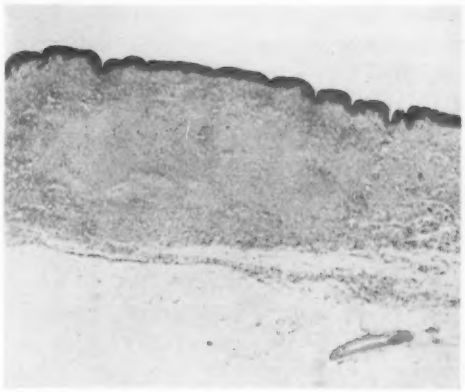

Fig. 2.—Low-power view of microscopic section of skin-test reaction shown in Figure 1. Note reaction limited to dermis and well circumscribed; reduced from mag. × 17.

CASE 4.—T. M. had an area of erythema 2.5 cm. in diameter and an induration 1 cm. in diameter within 48 hours after the skin-test inoculation. The erythema increased to a maximum of 3 cm. in the following few days. The whole reaction gradually subsided over the subsequent four months to a slightly depressed 0.6 cm. reddish area with a 2 mm. white central nodule. In this state it has persisted up to 10 months after the skin test.

In the remaining three positive reactions the skin-test lesions were slightly less and erythema and induration ranged from 0.5 to 1 cm. These faded within a week.

Case 3, B. T., allowed us to remove the skin test area eight months after the initial

Fig. 3.—Microscopic section of skin-test granuloma shown in Figures 1 and 2. Note palisaded epithelioid cells and Langhans' giant cells at periphery of necrotic collagenous tissue of dermis; reduced from mag. × 125.

inoculation of cat-scratch disease skin-test antigen. The others refused surgical intervention. The microscopic sections (Figs. 2 and 3) showed the central area of dermis to be occupied by a completely acellular eosinophilic necrotic mass of tissue, in which the ghost-like outlines of collagen fibers suggesting normal arrangement of dermis were seen. This necrotic mass had an irregular outline and in some regions looked as if it had formed from a coalescence of several similar foci. Palisaded irregularly at the periphery of the necrotic area were few to moderate numbers of epithelioid cells and a scattering of lymphocytes. There was a slight increase in vascularity just outside this region. There was no foreign material present, and nothing could be identified as foreign-body reaction. Multinucleated giant cells were seen occasionally in the palisaded epithelioid area, and these resembled the Langhans' type of giant cell.

COMMENT

The series of veterinarians tested here was small, because severe reactions to the skin-test material occurred. Nevertheless a significant number, 7 out of 28, or 25%, had positive skin tests. The veterinarians were purposely selected from all those in the San Francisco and Petaluma area who would voluntarily submit to skin testing. These two areas were chosen because the majority of cases of cat-scratch disease seen by me up to this time had come from these two regions. It should be emphasized that the skin-test material used was from the same batch of antigen that has been used to test 84 suspected cases of cat-scratch disease and has given 33 positive reactions in active cases and 51 negative reactions. One of the seven positive-reacting veterinarians was judged to have an active case when tested, but the other six gave no history which could be judged to be that of cat-scratch disease.

A comparison of the positive and negative groups of veterinarians showed no real differences which were statistically significant. Contrary to what might have been expected, the negative group showed a slightly wider range of inoculating skin trauma by animals. There was also more complement-fixation reaction to the supposedly related psittacosis-lymphogranuloma group of diseases in the serum from the few of the negative group of veterinarians tested. Such findings give no clue as to a possible reservoir of the etiologic agent, the transmitting host, or the character of the etiologic agent itself.

The excessive reactions to the skin test in four of the seven positive reactors, however, suggest a degree of hypersensitivity beyond that seen in the active cases of this disease. In order to check this, a follow-up was made of the 33 positive reactors in the active case group, and none gave a history of such a prolonged reaction. It was possible to check on 22 of the 33, and only one of these showed a slight persistance of reaction. In this case a little erythema could still be detected two months after the skin-test inoculation. Even this was not comparable to the four excessive responses described above. The possibility of such a distribution of prolonged reactions occurring by chance in the veterinarian group as compared with the patient group is about 1 in 700. However, prolonged reactions have been noticed by Daniels and McMurray, in the United States, and by Mollaret, in France, to occur in a few skin-tested patients. Nevertheless, such an occurrence of prolonged reactions as reported here, and the probable type of reaction as indicated by the one biopsied lesion, would suggest an increased sensitivity in veterinarians. One is tempted to infer that this hypersensitivity may likely be due to the constant contact that veterinarians may have with the etiologic agent and to suggest that this agent may be animal-born. The fact that some veterinarians are sensitive and others are not may best be explained on the basis of individual susceptibilities.

However, an explanation for the prolonged skin-test reactions in the veterinarian group probably involves more than veterinarian hypersensivity alone. The persistent granulomatous reactions, which arose from only moderate initial reactions, would suggest some continuous irritating stimulus.

This can be found in the suspension-type antigen, containing many fine particles, which was used in these tests. It seems likely that these particles were not completely removed from the inoculation site as a more soluble material would have been and, in remaining at the site, acted as a constant local source of antigen to react to high antibody titers or to react to possible sporadic increases in antibody titer due to veterinarian contact with the disease on several occasions during the prolonged reaction period. The possibility of a simple foreign-body reaction accounting for the whole picture seems remote, because the same batch of antigen used for 84 patients and 24 other veterinarians showed no such reactions in these 108 other tests. In addition, the one lesion examined microscopically showed no antigen particles present in the tissue and no foreign-body reaction. Instead, the microscopic picture suggested that the tissue reaction was more like that thought to be due to hypersensitivity.

It would have been well to have skin-tested a control group of normal subjects; however, scarcity of antigen from the same batch and the slight dangers involved in use of this antigen made it difficult to obtain an adequate sample. The 51 negative skin-test reactors, many of whom were later shown to have another type of specific lymphadenopathy, and the 33 positive reactors would seem to be suitable control groups as regards the incidence of the prolonged reaction type of skin test.

SUMMARY AND CONCLUSIONS

Seven of 28 veterinarians skin-tested for cat-scratch disease gave a positive reaction. Only one of these seven was thought to have active cat-scratch disease, and none gave an adequate history of having had the disease in the past.

There were no statistically significant differences between the positive and negative groups of skin-tested veterinarians as regard age, type and length of practice, animal contact, or inoculating trauma.

Four of the seven skin-test-positive veterinarians gave prolonged reactions, lasting from 8 to 10 months. One of these lesions was biopsied at eight months and showed a granulomatous reaction.

It is suggested that the veterinarians may have constant contact or sporadic but continual contact with the etiologic agent of cat-scratch disease and that this may produce an increased sensitivity in some of the more susceptible veterinarians.

Dr. Bernice Eddie, Assistant Director, Hooper Foundation, University of California, performed the complement-fixation tests, and Dr. Robert Mills, Stanford University Medical School, gave surgical and photographic assistance.

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Combined Anterior and Posterior Myocardial Infarction

An Electrocardiographic Study

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The electrocardiographic manifestations of multiple infarction of the myocardium are always interesting, frequently puzzling, and sometimes missed entirely. In particular, the studies of evolutions of patterns of combined anterior and posterior infarction are still inadequate and incomplete. Yet the coexistence of such a combined lesion is a fairly common pathologic entity and has been reported to be as high as 32.3%.[1]

There are many reports of the "neutralization" of abnormalities in the electrocardiogram when a new infarct succeeds an old one in the opposite wall.* It has been pointed out that in such cases the tracings demonstrate a decided improvement that may not be warranted by the clinical findings. These electrocardiographic neutralization effects are by no means uniform or complete, and very often it is possible to detect the residuals of an old infarct in tracings depicting a recent one. Furthermore, one sees patterns of combined or multiple infarctions of the myocardium of an extremely interesting, complex, and varied nature, as exemplified by the following three cases. It is hoped that the analysis of these cases will stimulate further interest in a subject potentially of great clinical value.

CASE 1.—E. P., a 63-year-old white man, was admitted to the hospital on June 9, 1953, because of severe, recurrent, substernal pain for the previous month. At about 10 p. m. the evening before admission, while resting at home, he suddenly felt a severe constricting pain in the midsternal region that lasted over an hour and required a hypodermic injection of ¼ grain (15 mg.) of morphine for relief. After a good night's rest he was very much improved. An electrocardiogram (Fig. 1*A*) at this time showed abnormally deep Q-waves in Leads 2 and 3, and a QT-pattern in Lead aV_F consistent with an old posterior myocardial infarction. In Leads V_3 to V_6, inclusive, there were symmetrical inverted T-waves suggestive of acute coronary failure or impending myocardial infarction. In view of these findings, the patient was urged to enter the hospital. The past history was significant in that the patient stated he had had two previous "heart attacks." In 1947 he had substernal pain and was hospitalized for three weeks, and a year previous to the present admission he had had a similar episode, for which he was again hospitalized.

Physical examination on admission revealed an elderly white man resting quietly in bed. Blood pressure was 122/80, pulse rate was 84/min., and respirations were 22/min. The significant findings were weak heart tones with a regular rhythm, bilateral basal lung rales, and a barrel-shaped chest. Results of laboratory studies, including a urinalysis, complete blood cell count, and blood chemistry studies, were essentially normal.

Clinical course: For several days the patient continued to have anginal pain and there were persistent crepitant rales at both lung bases. Treatment consisted of anticoagulants (phenindione [Danilone]), digitalization with digoxin, an occasional intramuscular injection of meralluride (Mercuhydrin), and oral doses of phenobarbital and papaverine. The patient improved slowly but steadily, and on the 30th day of hospitalization (Aug. 8, 1954) was discharged to convalesce at home.

The serial electrocardiograms in this case are shown in Figure 1. The tracing in Figure 1*B* shows a very small R-wave in Lead V_1, a QS-wave in Leads V_2 and V_3 and a deep Q-wave in Lead V_4. The ST-segment is elevated and rounded in Leads V_2 and V_3, and the T-waves are still negative in Leads V_2 to V_5, but to a lesser degree than in the previous tracing. There are sufficient changes now to warrant the additional diagnosis of an acute anterior myocardial infarction. In Figure 1*C* there is further evolution of the pattern of acute anterior wall infarction characterized by pronounced

* References 2-6.

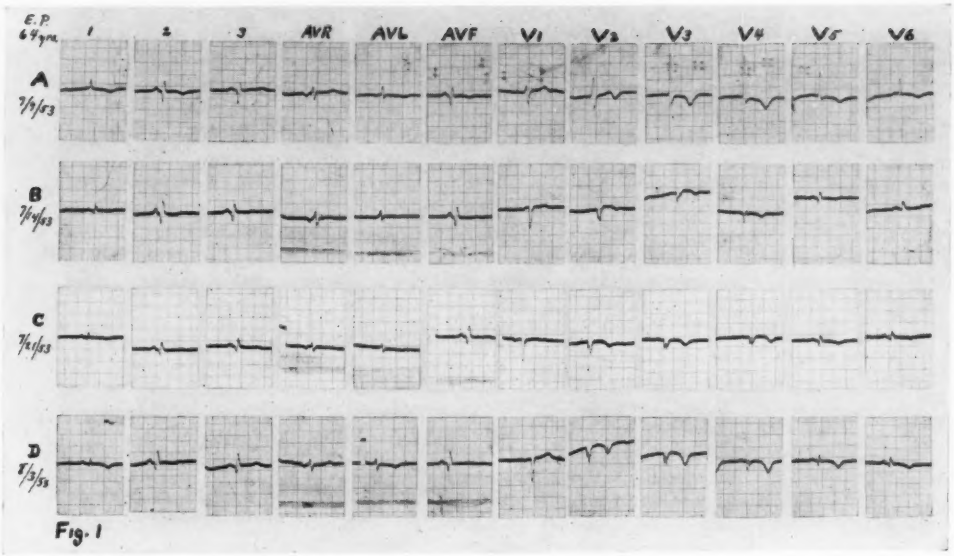


Fig. 1 (Case 1).—Serial electrocardiograms showing evolution of acute anterior myocardial infarction superimposed on an old posterior wall infarction. Residuals of the old posterior lesion are still present in the last tracing, taken on Aug. 3, 1953.

Q-waves and increasingly negative T-waves in nearly all the precordial leads. The signs of the old posterior wall lesion are now fading. The Q-waves in Leads 2, 3, and *a*VF are much smaller, and the T-wave in Lead *a*VF is now upright. The final electrocardiogram, in Figure 1*D*, shows a continued increase of the T-wave negativity in the precordial leads; otherwise, it is essentially unchanged. In summary then, the tracings show the evolution of an acute anterior myocardial infarction superimposed on an old posterior wall lesion, with some regression of the abnormal signs of the latter.

CASE 2.—T. L., a 69-year-old obese white man, was first seen on Nov. 10, 1954, complaining of substernal discomfort of one month's duration. The distress would occur after he walked two blocks but would pass off very quickly when he stood still for a few seconds. He persistently denied that it was a painful sensation, being able to describe it only as "unpleasant." It was felt under the sternum and did not radiate. There was no relation to meals, emotion, or cold. Dyspnea, orthopnea, and ankle edema were denied. The past history had been uneventful except for a thyroidectomy, in 1949, for thyrotoxicosis, from which there had been no recurrence.

On physical examination there were no positive findings other than hypertension (blood pressure 212/108) and obesity. The heart was not clinically enlarged; the rate and rhythm were normal, and the sounds were of moderate intensity. No murmurs were heard.

Fluoroscopic examination revealed clear lung fields and a heart shadow which was within normal limits. The thoracic aorta was slightly prominent and tortuous, but no aneurysmal dilatation was present. Routine urinalysis and serology revealed no abnormalities. An electrocardiogram (Fig. 2*A*) showed changes strongly suggestive of an anterior wall infarction probably of recent origin. The patient was urged to rest for the next four weeks, because the time of onset of his infarction could not be accurately determined. A low-sodium diet, reserpine, and sublingual tablets of glyceryl trinitrate (nitroglycerin) were prescribed.

The following night at 10:30 p. m. an urgent call was received. On the physician's arrival the patient was found to be pale and bathed in a cold sweat. He had been sitting in a chair talking when he was suddenly seized with a crushing substernal pain which soon spread to the neck and down both arms. The pulse was rapid and regular at a rate of 120; the blood pressure had fallen to 130/80 in both arms. The heart sounds were faint, but the lung fields were clear. After morphine was administered the pain soon abated and the patient's condition was much improved. He then volunteered the information that a week previously he had felt a severe substernal pain while taking a shower. The pain did not radiate and passed off in about 15 minutes. He was unable to explain why he had withheld this information the day before at the office. Hospitalization was arranged, and the following morning an electrocardiogram (Fig. 2*B*) re-

vealed the pattern of an acute posterior wall infarction superimposed upon the previous anterior wall infarction. The white blood cell count was 13,550, with 75% polymorphonuclear leucocytes. NPN was 35 mg.; fasting blood sugar, 118 mg.; cholesterol, 268 mg., and cholesterol esters, 113 mg. per 100 cc. The blood pressure was 140/85, and the patient was asymptomatic. Despite the fact that it seemed reasonably certain that the patient had had two episodes of myocardial infarction fairly close together, it was decided not to use anticoagulant therapy in view of the antecedent hypertension. An uneventful recovery was made, and the patient was discharged from the hospital at the end of the fifth week.

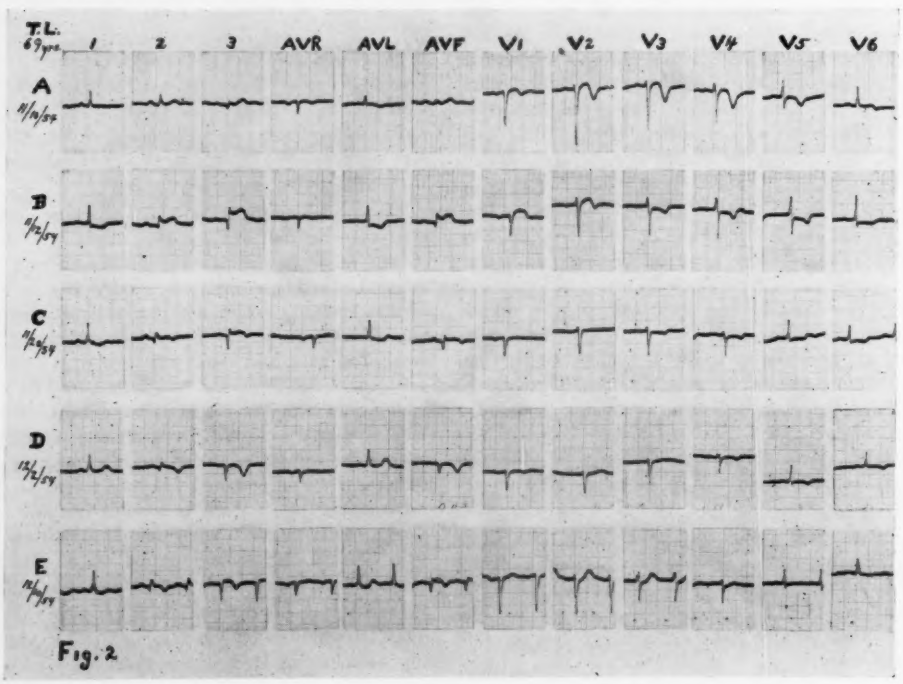
Serial electrocardiograms demonstrating the evolution of the patterns are shown in Figure 2. In Figure *2A* the precordial leads show QRS- (relatively small R-waves in Leads V_1 to V_4, inclusive), ST- and T-wave alterations strongly indicative of an anterior wall infarction. In Fig. *2B* the classic pattern of acute posterior wall infarction is now evident, and its progressive evolution through various stages is demonstrated in the serial graphs Figure *2B* to *2E*. Concomitantly, in the precordial leads the pattern of the anterior wall infarction progressively fades, until in Figure *2E* only the telltale low R-waves in Leads V_2 to V_4 and the flat T-wave in Lead V_5 remain as the last vestiges.

Case 3.—F. S., a 59-year-old white man, was admitted to the hospital on May 5, 1954, with a history of acute onset of precordial pain, dyspnea, and cyanosis. He was a known hypertensive for many years and two years ago had been admitted to another hospital for a heart attack that was diagnosed as an anterior myocardial infarction. In addition, there was a history of exposure to silica dust in the past. Fifteen days prior to admission he suffered an attack of precordial pain, from which he recovered spontaneously. On the morning of admission he had a recurrence of severe precordial pain associated with dyspnea and cyanosis.

Physical examination revealed the following: Blood pressure, 150/110; temperature, 100 F; pulse rate, 90/min.; respirations, 28/min. The patient was in mild shock with signs of pulmonary edema. Laboratory studies, including a urinalysis, complete blood cell count, and blood chemistry studies, were essentially normal except for 2+ albuminuria and a white blood cell count of 11,000.

A roentgenogram of the chest showed a nodular infiltration in both upper lobes that was suspected of being tuberculous. The heart size was reported as within normal limits. Sputum studies of three consecutive daily samples were negative for tubercle bacilli on two occasions.

Fig. 2 (Case 2).—This remarkable series of tracings shows typical evolution of acute posterior wall infarction with changes in the precordial leads, especially in Leads V_1 and V_2 of tracing *B*, which suggests a recent anterior wall infarction. In the precordial leads of tracing *E* there are still some residuals of the incompletely neutralized anterior wall lesion.



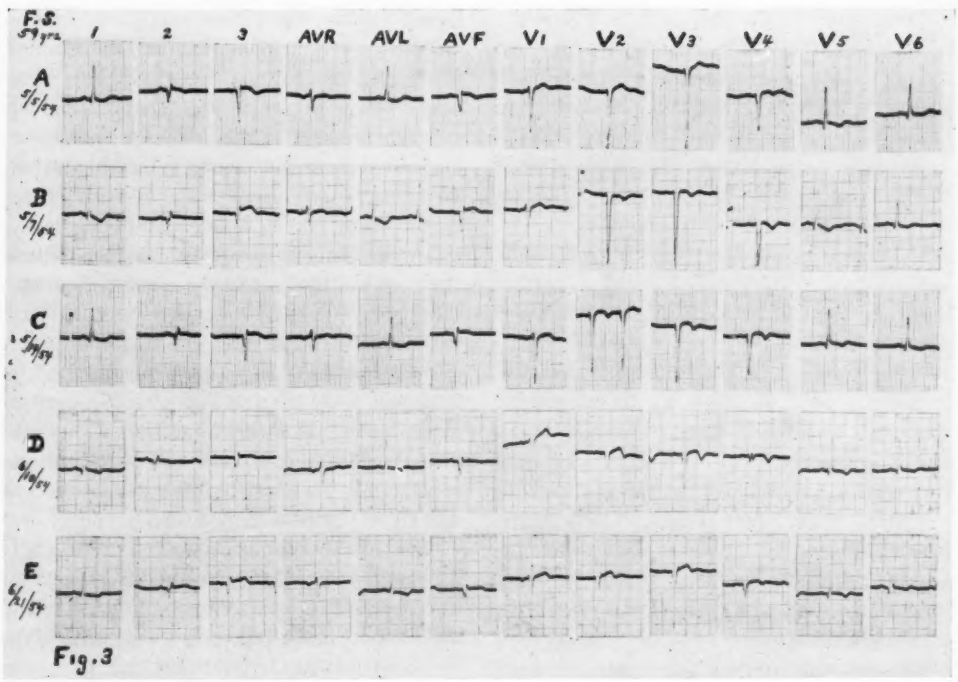


Fig. 3 (Case 3).—An interesting series of electrocardiograms demonstrating acute anterior and posterior myocardial infarction. Persistent ST-elevation in Leads *2*, *3*, and *a*VF in the last tracing may indicate a ventricular aneurysm of the posterior wall. Neutralization is incomplete, the residuals of the anterior wall lesion predominating. This may represent a simultaneous double acute infarction. The tracing in Figure 3*B* is slightly retouched.

Clinical course: During the first week the patient had fever that reached a maximum of 102 F associated with occasional bouts of coughing. The blood pressure on one occasion attained a maximum of 210/160. The therapy consisted of morphine and oxygen for the relief of precordial pain, Karrel diet, anticoagulants (ethyl biscoumacetate [Tromexan ethyl acetate]) and sedation. He was discharged on June 27, 1954, in comparatively good condition.

Figure 3 illustrates an interesting series of electrocardiograms taken in this case. The tracing in Figure 3*A* shows QRS- and ST-T-changes of an acute posterior myocardial infarction in Leads *2*, *3*, and *a*VF and a diminishing R-wave in the precordial Leads V_1 to V_4 and a negative T-wave in Lead V_4 consistent with the residuals of an old anteroseptal wall infarction. In Figure 3*B* and 3*C* there are sufficient serial changes in the precordial leads to warrant a diagnosis of an acute anterior wall infarction; persistence of the deep Q-waves and ST-T-changes in Leads *2*, *3*, and *a*VF are again consistent with an acute posterior myocardial infarction. In Figure 3*D* there is further evolution of signs of an acute anterior wall infarction, with some regression of the ST-T-changes of the acute posterior wall infarction. The time interval between this tracing and the previous one in Figure 3*C* is *27* days. In the last graph, Figure 3*E*, there is further regression of the signs of acute posterior myocardial infarction, characterized by upright T-waves in Leads *2*, *3*, and *a*VF. In addition, there are signs of regression of the T-wave changes of the anterior wall lesion in the precordial leads.

COMMENT

In each of these three cases there is sufficient evidence, both from the history and from the electrocardiogram, to justify a diagnosis of two distinct myocardial infarctions. Tracings of F. S. and E. P. (Cases 3 and 1, respectively) after they had recovered from their first episode of infarction are lacking; nevertheless, this does not prevent the analysis of those that were obtained. The frequently observed tendency toward neutralization of the electrical effects of an old myocardial infarct by a more recent one occurring in the opposite wall is demonstrable in these interesting electrocardiograms. However, the neutralization effect is not complete

in these cases. In the case of T. L. (Case 2), for example, there is still evidence in the last tracing of the older anterior wall infarction characterized by a diminishing R-wave from Lead V_3 to Lead V_4 and flat to diphasic T-waves in Leads V_5 and V_6. In the case of F. S. (Case 3) there are abnormal Q-waves in Leads 2, 3, and aV_F, representing the residual effects of the posterior wall infarction, and a QS-wave in Leads V_3 and V_4 with a negative T-wave in Lead V_4 and diphasic T-waves in Leads V_5 and V_6, which represent the residuals of the anterior wall lesion. In the case of E. P. (Case 1) the last tracing shows a QS-wave in Leads V_1 to V_4 and a negative T-wave in Leads V_2 to V_6 of anterior wall infarction, which tower above the remnants of the older posterior wall infarction manifested by the abnormal Q-waves in Leads 2, 3, and aV_F. The remarkable thing here is that, although there is overshadowing of the electrical effects of one infarction by those of a more recent one, there are sufficient residuals of the incompletely neutralized electrical forces to permit a diagnosis of double infarction. How long such residual changes will remain in a given case cannot be determined from this study. It is apparent, however, that a diagnosis of a recent infarction superimposed on an old one can frequently be made by serial electrocardiograms, and under certain circumstances such a diagnosis can be entertained on the basis of a single tracing. In addition to this tendency toward reciprocal neutralization of electrical effects in combined anterior and posterior wall infarctions, it is noted that the more recent infarction tends to obscure the electrical effects of the older infract and thus to dominate the electrocardiographic findings.[6]

Another interesting feature is the simultaneous development of electrocardiographic abnormalities consistent with a diagnosis of double acute infarction in opposite walls of the myocardium, as illustrated in the case of F. S. (Case 3). This impression could not be fully substantiated, as the patient survived, and consequently there was no pathological corroboration. From an electrocardiographic standpoint alone, however, there is strong evidence of a double acute infarction. Another likely explanation for the electrocardiographic pattern noted in this case might be the presence of a ventricular aneurysm in the area of the posterior wall lesion associated with the acute anterior wall infarction. In the case of T. L. (Case 2) there is also evidence to suggest a double acute infarction pattern. However, here the pattern is not so startling as in the case of F. S. and the history suggests that there was an interval of one week between the two infarctions. Wolferth and Wood [7] were probably the first to describe the electrocardiographic signs of acute anteroposterior infarction. They reported 10 cases in a series of 104 myocardial infarctions. Two of the 10 cases were confirmed by postmortem findings, which revealed an acute anterior wall infarction that extended around the apex to involve about one-third of the posterior wall. Wilson and co-workers [8] also reported a case with signs of a posterior infarction in the limb leads and of anterior infarction in the precordial leads. The patient died, but no necropsy was performed. There was evidence of an acute pattern in both the standard and precordial leads, manifested by ST-elevation in Leads 2, 3, V_2, V_3, and V_5. In their opinion, the electrocardiographic changes precluded the possibility that there were two infarcts differing in age. They further stated that the changes did not appear consistent with the presence of a single infarct extending from the posterior surface of the heart around the left margin onto the anterior wall, for the most striking changes in the precordial leads were in the middle of the series. They were unable to explain these findings satisfactorily but pointed out that apical infarction might give rise to electrocardiographic changes of this sort if the heart were in a vertical position. On the basis of these reports, it is evident that acute infarction of the anterior and posterior surfaces of the heart, whether as a single confluent lesion or as separate entities, is not unusual and can be diagnosed electrocardiographically.

There are several reports in the literature of the occurrence of recent infarction of the

anterior and posterior walls of the heart. Wolferth and Wood [7] reported an incidence of about 10%; Baer and Frankel [9] reported a 7% incidence; and Myers, Klein, and Hiratzka [1] reported 20 cases out of 161 pathologically localized infarctions, an incidence of about 12%. The latter authors have stated that such a lesion can be explained on the basis of an occlusion of the anterior descending coronary artery because this vessel frequently passes around the tip of the left ventricle to supply the posteroapical wall. They conclude that therefore a single arterial occlusion is sufficient to account for this condition. There may be an alternative explanation. Following an initial infarction, an area of ischemic muscle may recover with the establishment of a collateral circulation. This area of muscle is now viable and is dependent on this collateral circulation for its existence. If a second infarction in the opposite wall should develop owing to occlusion involving the artery upon which this collateral circulation is dependent, then the simultaneous development of a double acute infarction in opposite walls is inevitable. Thus a situation could arise in which two separate acute infarcts or a single, large confluent infarct may develop, with involvement of the anterior and posterior walls. Such a mechanism might explain the electrocardiographic patterns noted in Case 3. This concept will have to be verified by postmortem correlation; nevertheless, it seems to have considerable merit on the basis of our present knowledge.

SUMMARY AND CONCLUSIONS

An electrocardiographic study of three interesting cases of combined anterior and posterior myocardial infarction is presented. The well-known tendency toward neutralization or dominance of the electrical effects of a recent infarct over those of an old infarct is demonstrated. It is also shown that this neutralization effect is often incomplete and that the diagnosis of a double infarction in opposite walls can be suspected in many instances by careful analysis of even a single electrocardiogram. Serial tracings naturally increase our diagnostic accuracy in such problems. An interesting pattern of double acute infarction involving both the anterior and posterior surfaces of the heart is also discussed. A review of the literature shows that an acute or recent anteroposterior infarction is fairly common and has an incidence of approximately 10%. A new concept is offered to explain the occurrence of such a lesion either as a single, large confluent infarct or as two distinct lesions. A continued study of the correlation of these interesting electrocardiographic abnormalities with pathological findings seems warranted.

Dr. M. Sciorsci permitted us to use Case 3, and Mrs. Florence J. Chieffo, R.N., gave assistance in preparing the illustrations.

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Regurgitation Type of Jaundice During Prolonged Therapy with Chlorpromazine

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The appearance of jaundice following the administration of chlorpromazine (Thorazine) has been mentioned rarely in the literature.* Owing to the brief period in which this drug has been used, only a few patients with jaundice have been appraised regarding abnormal liver-function tests, systemic manifestations, course, duration, and prognosis. Therefore three cases of prolonged obstructive type of jaundice which were observed complicating therapy with this drug in three Omaha hospitals are reported below.

REPORT OF CASES

CASE 1.—Mrs. S. S., a 65-year-old white woman, was hospitalized on Feb. 11, 1954, with a diagnosis of postinvolutional depression. She had been a diabetic for 15 years, well-controlled with diet and insulin. There was no history of allergy or of liver or biliary tract disease. Examination on admission was noncontributory. She received electrical shock therapy followed by chlorpromazine, receiving a total of 3360 mg., the highest daily dosage being 200 mg. On the 23rd day of drug therapy she became jaundiced and the chlorpromazine was discontinued. She had a marked pruritus but developed no anorexia, abdominal pain, fever, or other systemic manifestations. The liver was not enlarged or tender.

Laboratory data on admission revealed normal hematological and urinary findings except for glycosuria. With the occurrence of jaundice there was no change in the hemoglobin, red blood cell count, white blood cell count, or differential count except for 7% eosinophiles on one occasion. Bile was found in the urine. There was a marked increase in the icterus index, which rose from 48 to 106 units. The alkaline phosphatase was 17.3 Bodansky units, and the cephalin-flocculation determination was normal. Complete data are given in the Table.

The patient was considered to have an extrahepatic biliary tract obstruction, and 38 days after the appearance of jaundice laparotomy was performed. At surgery the liver was slightly enlarged; the gall bladder and common duct were not distended. The common duct was patent, and no calculi were found. Liver biopsy was not done.

Subsequently the depth of jaundice slowly decreased, and at the time of dismissal the patient was still slightly icteric, with an icterus index of 60 units. She was anicteric 117 days after the appearance of jaundice.

CASE 2.—Mrs. L. H., a 65-year-old white woman, was admitted on Aug. 2, 1954, with jaundice and pruritus. She had a history of epigastric distress following meals with nausea and vomiting dating to 1948, the etiology of which had never been determined. No evidence of allergy or of liver or gall-bladder disease had been found in the past. Three weeks prior to hospitalization, because of an exacerbation of her symptoms chlorpromazine therapy was instituted, the patient receiving a total of 1350 mg., the largest daily dosage being 100 mg. After 15 days of treatment with improvement of her complaints, jaundice appeared and the drug was discontinued. She developed a marked pruritus but had no other symptoms. The urine was dark and the stools light in color.

Physical examination revealed a well-nourished elderly white woman, markedly icteric, with mul-

Read before the Mid-West Section of the American Federation for Clinical Research, Chicago, Oct. 28, 1954.

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Liver-Function Tests on Three Patients with Chlorpromazine Jaundice

Patient	Date	Icteric Index	Bilirubin, Mg.		Alkaline Phosphatase, Units	Cephalin Flocculation	BSP *	Thymol Turbidity	Albumin, Gm.	Globulin, Gm.	Cholesterol, Mg./100 Cc.	Cholesterol Esters, %	2 Hr. Urine Urobilinogen, Ehrlich Units	24 Hr. Stool Urobilinogen, Mg.
			Direct	Total										
Mrs. S. S., laparotomy 5/17.....	4/10	48	....	....	....	...	....	...	...	...	...	..	....	....
	4/20	73	....	....	....	...	....	...	...	...	...	..	....	....
	4/30	104.8	....	....	17.3	1+	....	...	...	...	...	..	....	....
	5/12	106	....	....	....	1+	....	...	...	...	...	..	....	....
	5/25	79	....	....	....	...	....	...	...	...	...	..	....	....
	6/12	60	....	....	....	...	....	...	...	...	...	..	....	....
Mrs. L. H., laparotomy 8/18.....	7/29	..	12.2	17.8	8.16	±	55.8	5.7	...	...	250	79	....	....
	8/ 6	..	35.4	48.6	10.8	±	....	6.3	3.3	3.4	...	..	0.06	3.49
	8/12	..	....	....	6.0	1+	....	4.4	3.5	3.4	...	..	....	....
	8/16	..	25.4	42.03	3.8	...	....	...	3.5	3.8	...	..	....	....
	8/18	..	17.8	30.5	....	1+	....	8.3	...	...	233	63	....	....
	8/24	..	14.2	22.2	....	...	....	...	3.3	3.5	...	..	....	....
	9/ 8	..	4.8	7.7	....	±	16	6.3	3.9	3.9	...	..	....	21.3
	9/20	..	5.8	8.2	....	2+	....	5	3.4	3.9	204	84	....	....
	11/ 7	..	1.4	2.0	2.4	1+	4.2	6.4	3.8	2.6	...	..	....	....
Mr. B. A. T., laparotomy 8/2.....	7/12	..	7.15	8.70	8.0	1+	35	1.2	...	...	...	..	0.43	....
	7/20	..	....	....	30.8	1+	27.5	3.9	3.4	3.3	...	..	....	....
	7/28	..	4.2	5.55	35.8	1+	....	...	...	...	584	48	0.36	....
	8/ 2	..	3.0	3.85	10.4	...	....	...	...	...	336	53	....	79
	8/10	..	1.8	2.6	13.0	0	....	1.0	...	...	135	52.2	....	....
	8/23	..	1.25	1.65	4.4	0	2.0	0.8	3.6	2.9	190	52	....	....

* Sulfobromophthalein.

tiple excoriations over the arms and chest. The abdomen was slightly distended, but the liver, spleen, and kidneys were not palpated.

The hemoglobin was 14.5 gm.; the white blood cell count was 5600, with a normal differential count. The urine was negative except for the presence of bile. A summary of liver-function tests is given in the Table. Three days after the onset of jaundice the direct-reacting bilirubin was 12.2 mg. and the total bilirubin was 17.8 mg. per 100 cc. (Method of Malloy and Evelyn). This increased to 35.4 mg. direct-reacting and 48.6 mg. total. A progressive decrease in the bilirubinemia was found on subsequent determinations. The alkaline phosphatase was increased to 10.8 Bodansky units; the cephalin-flocculation determinations were normal. There was a slight elevation of the thymol turbidity and also a mild increase of the serum globulins. The cholesterol and cholesterol esters were within the limits of normal. The two-hour urine urobilinogen was only 0.06 of an Ehrlich unit, and a four-day stool specimen revealed a fecal urobilinogen of 3.49 mg/24 hr. Repeated hematological determinations showed no variation except for 17% eosinophiles.

The patient had a progressive increase in her jaundice, with no additional symptoms. It was felt that the jaundice was secondary to chlorpromazine, but an extrahepatic biliary tract obstruction could not be ruled out, and she underwent surgery 25 days after the onset of icterus. The liver was slightly enlarged; the gall bladder and common duct were not distended, and the common duct was negative on probing.

Clinically the patient was improving at the time of surgery, and she continued to show a progressive decrease in the jaundice postoperatively. However, on her discharge, 60 days after the appearance of jaundice, she still had bilirubinemia of 8.2 mg. per 100 cc. When seen 25 days later she was still icteric. On Nov. 7, 108 days after the onset of jaundice, she had normal bilirubin determination.

On microscopic examination of the surgical liver biopsy specimen there were seen mild, nonspecific hepatocellular changes with slight variation in the size, shape, and depth of staining reaction in the parenchymal cells. Within the lobule scattered round-cell infiltration in the sinusoids was noted. The bile canaliculi were plugged with bile, with deposition of bile in the surrounding parenchymal cells. The portal areas showed some increase in cellularity but no fibrosis. The larger biliary channels did not contain bile, and there was no evidence of distention or obstruction (Fig. 1).

Case 3.—B. A. T., a 59-year-old white man with a chronic encephalitis since February, 1954, was admitted as a transfer patient on April 12, 1954. Blood titers for St. Louis, Eastern and Western,

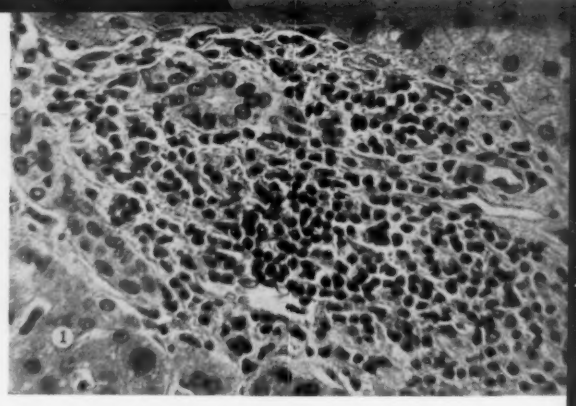


Fig. 1 (Case 2).—Liver biopsy specimen, showing hypercellularity with infiltration of lymphocytes and mononuclear cells. The larger biliary channels are normal.

and equine encephalitis were negative. Past history was negative for liver or biliary tract disease except for an episode of apparent infectious hepatitis in 1918, with no sequelae. In 1948 a gastric resection for duodenal ulcer was performed. No allergic history was obtained.

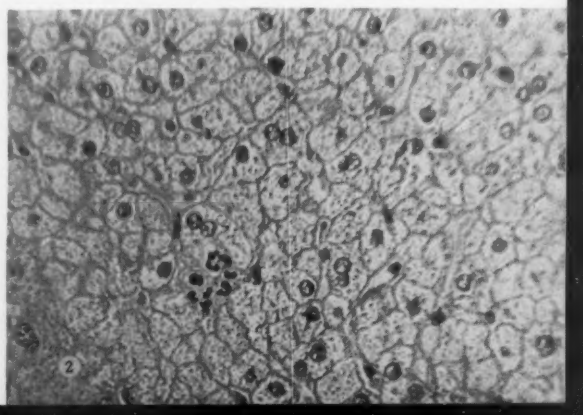
On examination he was confused and had confabulation and flight of ideas. The spleen, liver, and kidneys were not palpable.

The hemoglobin was 11 gm., with a red blood cell count of 4,100,000 and a hematocrit value of 48%. The white blood cell count was 10,500, with a normal differential count. Urinalysis and serology were negative. The total protein and white blood cells in the spinal fluid were increased to 76 mg. per 100 cc. and 31 per cubic centimeter, respectively, and the colloidal gold curve was 1233333210.

He ran an intermittent low-grade fever, from 99 to 100.1 F, with a gradual, progressive weight loss of 43 lb. (19.3 kg.). Nicotinic acid, thiamine, and multivitamins were given during this course, with no improvement. Because of marked agitation chlorpromazine was started on June 7, with a total dosage of 1520 mg., the highest daily dosage being 50 mg. Thirty-one days later he became jaundiced and the medication was stopped. He had a marked pruritus but no other subjective symptoms. The liver was palpable 2 cm. below the subcostal margin and was smooth and slightly tender on first percussion. Fever disappeared while the patient was still jaundiced.

Hematological studies showed no variation, no eosinophilia being noted. The first bilirubin de-

Fig. 2 (Case 3).—Localized area of necrosis with collection of neutrophiles.



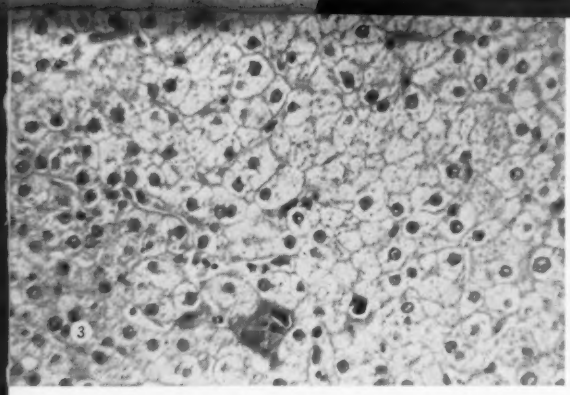


Fig. 3 (Case 3).—Liver biopsy specimen, with plugging of the bile canaliculi with bile thrombi and deposition of bile in the surrounding parenchymal cells.

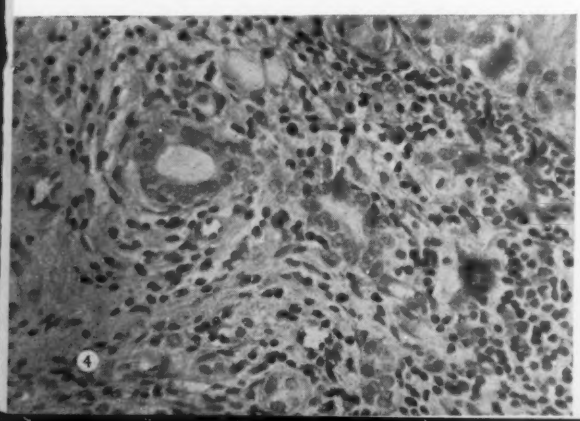
termination was 7.15 mg. per 100 cc. direct-reacting and 8.70 mg. total. Repeated determinations showed a progressive decrease, as shown in the Table. The alkaline phosphatase increased from 8 to 35.8 Bodansky units. The cephalin-flocculation and thymol-turbidity determinations were normal. He had a slight elevation of the serum globulin and a marked increase in the total cholesterol to 584 mg. per 100 cc. The cholesterol esters were reduced to 48%. The 2-hour urine urobilinogen and 24-hour fecal urobilinogen were within the limits of normal.

The clinical impression was that the patient had chlorpomazine jaundice; however, surgical jaundice could not be excluded and the patient underwent laparotomy 24 days after the onset of jaundice, at which time the patient was showing clinical and laboratory improvement.

The liver was enlarged at surgery. The gall bladder and common duct were slightly distended. On probing, a partial stenosis of the distal common duct was considered to be present; however, when the duodenum was opened a free flow of bile was seen. A choledochoduodenostomy was done, and the gall bladder was removed. Within the gall bladder there was a calculus 2 cm. in diameter. No other calculi were found.

The patient continued to show a progressive decrease in jaundice after surgery, becoming anicteric 55 days after the onset of jaundice, with a serum bilirubin of 1.65 mg. per 100 cc.

Fig. 4 (Case 3).—Portal area. No evidence of distention or obstruction of the biliary channels is seen. There is round-cell infiltration with lymphocytes and monocytes.



A liver biopsy specimen taken at surgery showed mild variation in the size, shape, and staining reaction of the parenchymal cells. Within the lobule were areas of cellular infiltration in small necrotic foci. No eosinophilia was seen (Fig. 2). There was prominent plugging of the bile canaliculi with bile and bile deposition in the surrounding parenchyma (Fig. 3). A slight hypercellularity of the portal areas was seen, but no fibrosis. The larger biliary channels were not distended and did not contain bile (Fig. 4).

COMMENT

While receiving chlorpromazine three patients developed protracted jaundice with laboratory findings compatible with obstruction of the extrahepatic biliary tract but with no systemic manifestations except pruritus. The liver was palpable in only one patient. Each had hyperbilirubinemia, elevated alkaline phosphatase, and normal cephalin-flocculation determinations. Evidence of probable mild parenchymal damage was noted in the slight elevation of the thymol turbidity in one and in the serum globulin in two of the patients. Cholesterol determinations were done in two of the cases; in one the determination was normal; in the other there was hypercholesterolemia with a decrease in the cholesterol esters.

Surgical jaundice could not be excluded by laboratory or clinical studies, and all three patients underwent surgery, with no findings of obstruction in two. In the third case the prior existence of a transitory stone in the common duct could not be completely excluded. Liver biopsies in Cases 2 and 3 showed similar findings, with bile stasis in the biliary canaliculi. Within the lobule there was a mild nonspecific cellular infiltration. The portal triads had a slight monocytic and lymphocytic infiltration, with no evidence of obstruction or distention of the larger biliary channels.

These cases are similar to the jaundice seen in cholangiolitic hepatitis. However, lack of systemic manifestations and the occurrence during therapy with a common drug would appear to eliminate this diagnosis. Thiouracil, sulfonamide, methyltestosterone, arsphenamine, carbon tetrachloride, and

chloroform anesthesia have also been observed to cause a regurgitation jaundice with only minimal evidence of hepatocellular damage.† None of these drugs was administered to the patients prior to the appearance of their jaundice.

These patients were of extreme interest since clinical and experimental studies in both humans and animals have shown little evidence of hepatic toxicity with chlorpromazine, even in patients with known liver disease.‡ Lehnmann and Hanrahan,[1] however, have reported mild changes in cephalin-flocculation and serum protein determinations in patients with no known liver disease when this drug was given. Transitory jaundice often accompanied or preceded by pyrexia has been observed.§ The jaundice cleared within one to two weeks after the withdrawal of chlorpromazine. Reintroduction of the drug was noted to cause no reappearance of the jaundice. The mechanism causing jaundice remains obscure; however, the presence of eosinophilia suggests hypersensitivity. Allergic manifestations consisting of urticaria, asthma, and maculopapular rashes have been noted with the use of this drug.‖

Azima and Ogle [5] have noted two cases of prolonged jaundice occurring during chlorpromazine therapy lasting for over two months. Detailed description of the complication has been recently reported in four other patients, the jaundice persisting 16, 39, 40, and 120 days, respectively.¶ Laboratory findings were similar to those described in this report, presenting evidence of an obstructive jaundice. In contrast to the lack of symptoms in our patients, three of those reported had prodromal symptoms of malaise, anorexia, and nausea, while two had fever.

Clinical and laboratory findings do not rule out the presence of an extrahepatic obstruction. However, the history of therapy with chlorpromazine, prodromal symptoms, fever, and the appearance of eosinophilia are helpful in confirming the diagnosis of medical jaundice.

CONCLUSION

Prolonged regurgitation jaundice is described in three elderly patients under therapy with chlorpromazine. Pruritus was the only significant symptom. Clinical and laboratory findings did not distinguish these cases from extrahepatic surgical jaundice, and all three underwent laparotomy. In two there was no evidence of obstruction. In the third this possibility was not completely eliminated. The liver biopsies in two showed inflammatory cell infiltration within the lobule, minimal liver cell changes, and bile plugging of the bile canaliculi. There was a slight increase in the cellularity of the portal triads, with no evidence of obstruction of the larger biliary channels. The mechanism of this complication is unknown.

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Treatment in Internal Medicine

TREATMENT OF ACUTE RENAL SHUTDOWN

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WHEN THE occurrence of anuria or oliguria leads to a diagnosis of acute renal shutdown the physician must not only plan appropriate supportive therapy but must at the same time institute any measures which might reverse the process which has led to diminished urine flow. Unless there is virtual certainty that the cause resides within the kidney, investigation of the entire urinary tract is obligatory, since obstructive lesions may occur at any site. Stones as well as neoplasms can obstruct both ureters simultaneously or successively. Persons who, as a result either of disease or of developmental anomaly, have only one functioning kidney will develop apparent acute renal shutdown as the result of obstruction to the sole ureter.[1]

Dehydration, with or without salt depletion, is one of the commonest causes of oliguria encountered today. Pure water depletion without electrolyte loss generally leads to a concentrated urine. However, when there is any question as to whether such a state is responsible for oliguria it is a simple matter to insert a catheter in the bladder, determine urine flow, and then administer 1 liter of a 5% dextrose or fructose solution intravenously within a period of 30 to 60 minutes and ascertain the effect on the rate of urine formation.

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The authors are indebted to Dr. Reed M. Nesbit, Editor, and to Charles C Thomas, Publisher, Springfield, Ill., for permission to abstract parts of a monograph entitled *Clinical Management of Renal Failure,* which will be published next autumn in the American Lecture Series.

Acute "renal" shutdown (acute renal failure associated with oliguria or anuria) may be due to reversible or irreversible lesions. Although the lesions of bilateral renal infarction and acute cortical necrosis are presumably irreversible, the diagnosis can rarely be made with certainty and treatment should be supportive until there is unequivocal evidence that the lesion is an irreversible one. The reversible group includes acute glomerulonephritis and hemorrhagic papillary necrosis as well as acute tubular necrosis (lower nephron nephrosis, hemoglobinuric nephrosis, shock kidney, crush kidney, etc.). In these cases many specific forms of therapy are indicated, depending on the etiology of the lesion: For example, penicillin, digitalis, and antihypertensive therapy are often required in acute glomerulonephritis; in papillary necrosis the offending organism must be combatted with an appropriate antibacterial agent and, in addition, treatment of the associated diabetes and/or urinary tract obstruction is essential. Among the many causes of acute tubular necrosis, as yet only mercury (and possibly other metallic) poisoning can be specifically counteracted with early administration of the specific antidote—dimercaprol (BAL). Since shock is so important an etiologic factor in many cases of acute tubular necrosis, it is axiomatic that restoration of blood volume is essential. When blood has been or is being lost the obvious replacement fluid is blood. (Until blood is available and cross matched, isotonic saline should be employed.) Replacement of blood loss may well prevent or minimize the development of acute tubular necrosis.

Not only blood and plasma loss but electrolyte and water losses must be replaced at the outset. Although pure water deficit leads to both cellular and extracellular dehydration, whereas a deficiency of water and salt in isotonic proportions leads to extracellular

dehydration alone, we are unable to differentiate between these two conditions from inspection of the patient. However, the history of preceding events almost always gives significant information. Since gastrointestinal secretions are isotonic or nearly so, the patient who has lost fluid from any portion of the gastrointestinal tract requires either isotonic sodium chloride or a sodium chloride-sodium lactate replacement solution, the latter if small-intestine, biliary, or pancreatic juice has been lost. If water intake has been limited there will be an additional deficit of pure water. In patients in whom replacement of gastrointestinal losses has been accomplished by water alone, there may be pure salt deficiency, necessitating replacement with hypertonic sodium solutions. It is in situations of this sort that determination of the serum concentration of sodium, chloride, and bicarbonate will be most useful. It should be borne in mind, however, that such analyses reveal only composition, not volume.

Once all the necessary measures to remove or alleviate the cause of renal shutdown have been taken, the remainder of treatment consists in sustaining life until such a time as renal function returns.[2] This in essence consists in combating the physiologic consequences of renal failure, regardless of the etiology of the latter.

These consequences result largely from the loss of two important renal functions: the function of maintaining a relatively constant volume and composition of the extracellular fluid and the function of removing certain products of catabolism which are no longer required by the body. In acute renal shutdown these tasks devolve upon the physician. By assiduous control of what is allowed to enter the body he can not only maintain the volume of the extracellular fluid reasonably constant but also in a measure prevent marked change in its composition. Further, he may diminish the rate of accumulation of catabolic products by limiting protein breakdown. The importance of the last derives from the fact that in protein catabolism the oxidation of organic sulfur and phosphorus leads to the accumulation of sulfate and phosphate anions as well as their attendent cations, including hydrogen ions. Serum bicarbonate concentration and pH tend to fall. With a rising serum phosphate level, serum calcium concentration likewise declines. In addition, protein catabolism leads to the release of cell potassium and of various nitrogenous moieties, chief of which, from a quantitative viewpoint, is urea. There is considerable evidence that urea itself is not responsible for any of the important manifestations of uremia. The concept that the accumulation of unknown nitrogenous products of protein catabolism is responsible for such manifestations has long been held but remains no closer to proof than when first advanced. On the other hand, it is abundantly clear that potassium intoxication by its effect on the heart is a potential threat to life in acute renal shutdown. This has been particularly true in seriously wounded Korean-battle casualties who had extensive tissue damage and who received many units of relatively old bank blood (with an initially elevated serum potassium level) in the process of resuscitation.[3] Under these and similar circumstances in civilian practice physiologic methods alone may fail to control the accumulation of potassium in the extracellular fluid and may also be insufficient to prevent gross distortion of its composition and/or volume. In such situations it becomes imperative to employ measures which can remove materials from the body. Just as the prevention of oligemic shock and hemolytic transfusion reactions serves to diminish the incidence of acute renal shutdown, so the employment of proper physiologic measures in the face of oliguria will serve to diminish the need for, and frequency of, employment of artificial means to remove materials from the body.

PHYSIOLOGIC MEANS OF TREATMENT

When the patient with acute renal shutdown is first seen, while extrarenal factors are being investigated, an endeavor is made to restore any deficits of salt, water, red blood cells, or plasma which are present. Overcorrection must be avoided scrupulously. If at this time the patient has already

received excessive water, this may be overcome eventually by virtue of daily insensible evaporative loss. However, excessive salt can only be eliminated by one or another artificial means.

In preventing overhydration the best guide is the daily weight of the patient. Once the initial replacement of deficits has been accomplished, there should never be a gain in weight. Rather, since the patient is metabolizing several hundred grams of body tissue daily for his metabolic needs, a loss of several hundred grams (½ to 1 lb.) daily is most consistent with proper water balance.

A nonfebrile 70 kg. patient resting in a temperate environment, not sweating, has an insensible loss of water from skin and lungs amounting roughly to 1000 ml. per day. Preformed water and water of oxidation of body fat and protein should amount to somewhat over 400 ml. daily, thus leaving a water deficit of approximately 500-600 ml.

Endogenous protein catabolism in such a resting patient receiving no exogenous nutriment amounts to approximately 1 gm. per kilogram of body weight, or 70 gm./day. This breakdown of protein will be increased by activity, fever, infections, tissue necrosis, and, in patients with postoperative or posttraumatic oliguria, by the so-called metabolic response to injury. Measures which minimize these factors will retard the development of acidosis and potassium intoxication. Hence a bed and chair regimen is advocated for patients with acute renal shutdown. Since the remainder of the caloric requirement in such a patient must perforce be met by burning body fat (the meager glycogen reserves of the body will be catabolized within the first 24 hours), ketosis will shortly appear and will add to the acidosis associated with inorganic ion retention. If, however, as little as 100 gm. of dextrose is administered daily in divided doses, not only will ketosis be eliminated but endogenous protein catabolism will be reduced by almost one-half. Thus the rate of accumulation of sulphate, phosphate, potassium, and urea due to protein catabolism will likewise be halved. Further increasing the carbohydrate intake adds so little additional sparing of endogenous protein that the gain is seldom worth the difficulties involved. Whether there is any benefit derived from supplying exogenous fat rather than permitting the catabolism of the patient's own fat stores seems doubtful. To be sure, the latter procedure leads to a reduction in the amount of body fat, and this, in an already emaciated patient, might be inadvisable. However, most patients seem to suffer little from the loss of 5 to 10 or more pounds of body fat. Fat emulsions satisfactory for intravenous use remain to be perfected. At present the high incidence of adverse reactions precludes their use. Mixtures of peanut oil and sugar, employed either orally or via an indwelling Levin tube, have been extensively used by Bull and co-workers.[4] When tolerated, such mixtures minimize endogenous fat catabolism. However, even with tube feeding there is often vomiting and diarrhea. Both result in variable losses of water and electrolyte, which are difficult to replace. Because of the high incidence of vomiting, we have preferred to order nothing by mouth during most of the oliguric phase. This policy also avoids the danger of patients inadvertently receiving excessive fluid or foods containing potassium.

Theoretically, the patient should receive a basic ration of approximately 500 ml. of 20% dextrose in water, divided into two 250 ml. portions given roughly 12 hours apart and each administered over a period of several hours. Practically, there arises the problem of venous thrombosis with dextrose in 20% or higher concentration, although this can be obviated by inserting a plastic tube through a peripheral vein and advancing it to the vena cava. Through such a tube 50% dextrose solutions can be administered with a lessened danger of thrombosis. However, we have preferred to give the daily 100 gm. of dextrose in 15% solution even though this necessitates the administration of a slightly larger amount of water. In addition, provided the patient's serum sodium and chloride values are normal at the time, all other fluid losses are replaced by a solution qualitatively similar to the fluid lost,

determined either by direct analysis or estimated from a knowledge of its source. Thus each day an amount of fluid approximating the preceding day's urine volume, whenever the latter is more than 100-200 ml., is given intravenously. In the absence of precise analysis, it is assumed that such urine approximates isotonic saline in composition. Similarly, losses through emesis, diarrhea, sweating, or extraneous drainage are replaced. For example, emesis is replaced with an equivalent amount of isotonic saline; wound drainage, with an equivalent amount of mixture of two parts of isotonic saline to one of isotonic (⅙ M) sodium lactate. Estimated sweat losses are assumed to be roughly one-half strength isotonic saline. Dextrose may be added to all fluids given to render the concentration 10%.

Not infrequently, when first seen, patients suffering from acute renal failure will exhibit significant lowering of serum sodium concentration as a result of their already having received excessive quantities of water. In such cases the careful and judicious administration of 5% sodium chloride, or of an appropriate mixture of such a solution with 1.0 M sodium lactate or bicarbonate, may benefit the patient by overcoming intracellular overhydration but entails the risk of unduly expanding extracellular fluid volume. Drastic restriction of fluid intake will accomplish the same end without expanding volume by virtue of the daily insensible loss of pure water through the skin and lungs. Indeed, in recent years we have not encountered any patients with such a degree of hyponatremia that any management other than drastic fluid restriction was required.

Tetany is rarely a problem in the management of acute renal failure, since the concomitant acidosis tends to protect the patient from overt manifestations. However, should these occur calcium should be given intravenously.

Should hyperkaliemia become threatening, while waiting for the application of the "artificial" means of treatment discussed below, one may attempt to diminish temporarily the toxicity of the high potassium level. Elevation of the serum calcium level counteracts the toxic effect of high potassium concentrations in animal studies, and temporary benefit has been reported from clinical use of calcium in large doses.* Raising the serum sodium concentration has a somewhat similar antagonistic effect, but unless serum sodium levels are initially low this procedure does not appear very useful in anuric patients. The combination of 50 to 100 gm. of dextrose together with approximately 1 unit of regular insulin for each 2 gm. of dextrose has been employed with most success.† The dextrose is given intravenously as a 10% to 25% solution, depending on the over-all fluid requirements of the patient. The rationale of the procedure lies in the known fact that when dextrose is deposited in the tissues potassium is removed simultaneously. Its effect, although transitory, may persist for several hours, during which time more effective means for lowering serum potassium may be readied. In our opinion, electrocardiographic signs of serious potassium intoxication remain the one unchallanged indication for the employment of artificial means of treatment.

After the stage of oliguria the urine volume may become excessive, as a result of various factors. First, tubular function with regard to reabsorbing electrolytes is more or less deficient and a concentrated urine cannot be elaborated. In addition, there is in these cases a large load of urea for excretion and, in some instances at least, an excess of salt and water in the body. Thus, added to the tubular defect there is the osmotic diuretic effect of the urea load and the salt and water load. If the body through normally acting mechanisms is striving to excrete the excess salt and water load and if the physician is quantitatively replacing the urinary losses, it is obvious that the polyuria will continue. The polyuria adds to the already present potential threat of excessive potassium loss in the urine, since even the normal kidney has a limited capacity for conserving potassium and cannot secrete a urine with a potas-

* References 5 and 6.

† References 5 and 6.

sium concentration much below that of extracellular fluid.

We maintain fluid and electrolyte balance (employing the oral route as soon as feasible) until the urine volume reaches 3 to 4 liters daily, at which time, being fully cognizant of the dangers of dehydration consequent to obligatory polyuria, we endeavor to judge the response to modest restriction of salt and water. If there is any indication suggesting that the polyuria is leading to an actual depletion of extracellular or plasma volume, additional intake, either by mouth or vein, is provided at once. Serum potassium levels are followed daily, and as soon as normal values obtain fruit juices are allowed at libitum and, in the event that the serum potassium falls below 3.5 mEq/liter, potassium citrate is given by mouth in doses of 3 to 5 gm. dissolved in water or fruit juice three or four times daily. If oral intake is precluded, potassium chloride may be added to other intravenous fluids in such amounts that the concentration does not exceed 30 mEq/liter. Ninety to 120 minutes should be taken in infusing 30 mEq. of potassium, in order to avoid the danger of unduly elevating the serum level. It is rarely necessary to infuse more than 30 to 60 mEq. of potassium daily.

ARTIFICIAL METHODS

Any rational discussion of the use of artificial methods for the maintenance of homeostasis during acute renal failure must be set against the background of the results of the physiologic methods of treatment already outlined. The reduction of mortality made possible by rigid adherence to physiological principles requires that any further measures enhance the results of such therapy and add no new serious risk. Unfortunately, controlled studies of the efficacy of artificial measures are neither possible nor indeed necessarily justifiable. Thus we are faced with the difficult task of evaluating techniques for treating a condition, "uremia," the precise nature of which is unknown. Death and disability in acute renal shutdown may be due to (1) failure of maintenance of a relatively constant composition and volume of the internal environment of the patient; (2) the accumulation of metabolic products; (3) nonrenal disorders which may have initiated or complicated the episode of acute renal shutdown and which may be aggravated in turn by (1) and (2).

The physiologic methods of treatment outlined above are chiefly concerned with the prevention of disturbances in the volume and composition of the body fluids; once dislocations have developed such therapy cannot easily reverse them, except for the correction of deficits by the addition of water, sodium chloride, etc. On the other hand, one or another of the artificial measures discussed below can theoretically subtract excessive water or electrolyte as well as remove any accumulated "toxic" material which is not fixed to tissue cells. Their efficiency and accuracy in performing these tasks is limited, however, and attended by some risk.

Exchange Resins

As presently employed, cation exchange resins in the ammonium, hydrogen, or sodium phase ‡ are administered either orally or by rectum in order to exchange for potassium.§ The method has been successful in removing as much as 75 mEq. of potassium in one day and in lowering the serum concentration from values over 8 mEq/liter to normal in one to three days. The recommended dose is 50 gm. a day by mouth or by retention enema. Small oral doses every one or two hours can be used to avoid nausea and allow greater dispersion throughout the intestine. An important disadvantage of this procedure is that ammonium- and hydrogen-loaded resins increase acidosis and sodium-loaded resins may contribute to undesirable extracellular fluid expansion. Gastric intolerance often precludes their use by mouth; administration by rectum is highly uncertain and may lead to fecal impaction. Their relatively slow ac-

‡ All the resin preparations available commercially in this country are intended for sodium removal and are preloaded with potassium. Potassium-free resins can only be obtained for investigative use.

§ References 7-9.

tion makes exchange resins unsuitable for emergencies, and thus most authors suggest their use as a prophylactic measure whenever the serum potassium level exceeds 6.0 mEq/liter. Therapy should be discontinued when the plasma potassium concentration falls below 5 mEq/liter or the urine flow rises above 500 ml/day. Special care must be taken to avoid the development of hypokaliemia during the diuretic phase, since the removal of potassium will continue well after oral resin administration has been stopped.

Exchange Transfusions

Much of the work with exchange transfusions has been done in France and Italy. The techniques vary from the use of small alternate venesections and transfusions to continuous exchange between a donor and recipient by cross transfusion or cross circulation. The intermediate method of exsanguinotransfusion or replacement transfusion as employed in the therapy of erythroblastosis fetalis has been widely used in France. Dausset's report [10] indicates that results are comparable to those obtained by physiologic methods alone. He used three to four exchanges of one or two blood volumes each and achieved a 65% recovery rate in 20 cases of varied etiology and a 70% recovery rate in 24 cases with acute renal failure following septic abortions. Potassium removal is inconsequential. With an initial level of 7.0 mEq/liter and an average level in the infused blood of 4 mEq/liter, only 3 mEq. of potassium would be removed per liter of blood exchanged, and, insofar as the blood given is generally not fresh, additional amounts of potassium far in excess of that removed might shortly be released from red cells.

Except for the simplicity of the procedure, the only advantages of exchange transfusions over methods using dialysis is a theoretical one with no present basis in fact—that there are toxic nondiffusible materials in the blood of patients with acute renal failure, the removal of which will save their lives. To outweigh this advantage are the disadvantages that (1) excessive variation in the patient's blood volume may lead to shock or pulmonary edema; (2) transfusion reactions may occur at a most unwelcome time; (3) with the use of multiple donors, the incidence of serum hepatitis will be high, and (4) there is a lesser removal of diffusible material than with dialysis.

Intestinal Lavage

Although the concept of intestinal lavage is an old one, the potential usefulness of the technique has only been realized recently.[11] Successful intestinal lavage requires the selection of a portion of the bowel whose absorption, excretion, and diffusion characteristics are fairly uniform and the administration of a fluid which will prevent water and electrolyte absorption by the intestine. In essence, a more or less controlled diarrhea is instituted, which can effectively remove potassium, water, and urea from the body but which is not as efficient in removing creatinine and uric acid, and perhaps therefore other potentially toxic constituents.

The advantages and disadvantages of intestinal lavage are readily apparent. It is the only procedure by which one can remove substantial amounts of urea, electrolytes, and fluid from the body without special apparatus or surgery. The chief disadvantage is that this removal is not precise and controllable but depends on the activity of the intestinal mucosa rather than on the concentration of the dialysing fluid alone. Practical limitations are encountered also. Vomiting and abdominal distention may develop during prolonged lavage. The passage of a tube into the small intestine may be poorly tolerated. Further it requires some time for the tube to reach a level adequate for perfusion. For the removal of potassium, however, only a small segment of bowel is required. Hicks and co-workers [12] were able to remove 30 to 150 mEq. of potassium per day by means of a tube which had passed through only two feet of small bowel. Alwall's technique [13] of simply purging the patient with magnesium sulfate has the advantage that no large volumes of fluid are introduced. It may be a useful and benign procedure early in the course of acute renal failure when the patient has been given too much fluid.

Although careful studies of intestinal transfers may ultimately permit the use of lavage with some assurance, at present its usefulness is limited to those situations in which physiologic methods of treatment and exchange resins are not effective and in which both external dialysis and peritoneal lavage are contraindicated. We have yet to encounter a case in the literature which fulfills these criteria, especially since the chief contraindication for peritoneal lavage, recent abdominal surgery, is also in general a contraindication to intestinal lavage.

Peritoneal Lavage

The emergence of acute renal failure as a major clinical entity during World War II was the stimulus for the widespread use of peritoneal lavage in the immediate postwar years (1946-1949).‖ Since the technique was often used in lieu of, rather than in conjunction with, physiologic means of therapy, the results were poor. Peritonitis and pulmonary edema were frequent, often fatal, complications. From the beginning there were wide variations in technique. The most appropriate composition of the dialysing fluid, the most appropriate length of therapy, and the use of intermittent versus continuous lavage were all difficult problems.

After an initial experience in which the complications appeared to outweigh the advantages, peritoneal dialysis has been improved to a point where it must be considered a useful and potentially life-saving procedure in acute renal failure. With the use of either intermittent [16] or short-term continuous lavage [17] with plastic catheters appropriately placed and a dialyzing fluid of appropriate composition, peritoneal lavage appears to serve the purpose of removing retention products and correcting body fluid abnormalities without undue risk. We are unable to evaluate the relative merits of intermittent *vs.* short-term continuous dialysis. Peritoneal lavage is of course contraindicated when there is an abdominal wound or infection.

‖ References 14 and 15.

External Dialysis

Although the principles of extracorporeal dialysis of the blood in uremia were fully worked out by Abel, Rowntree, and Turner in 1914,[18] it was not until 1943 that Kolff first introduced a practical dialyser for human use.[19] In the last 10 years a variety of new dialysers has been introduced. In this country the Kolff apparatus has been used extensively as refined by Merrill and others,[20] and a new type, first developed by Skeggs and Leonards,[21] has undergone extensive clinical trial.

The Kolff artificial kidney in its present state of refinement has certainly fulfilled the positive criteria for a good dialyzer. It can accept a large blood flow from the patient, pass it along a large dialyzing surface, and equilibrate it with a dialysing fluid which can remove large quantities of solutes. The apparatus is not ideal, however: 1. The ratio of the volume of blood in the machine to the dialyzing surface is fairly high, requiring "priming" of the machine with bank blood. If blockage occurs, the cellophane tube distends with blood and fatal "hemorrhage into the machine" can develop. 2. The apparatus is bulky, complex, and expensive. It cannot be transported to the patient, and its ideal operation requires a team of trained personnel who must devote much of their time to the application of dialysis in clinical and experimental problems. 3. The apparatus is not suited for the removal of fluid from the body. Although water will diffuse into a hypertonic dialysing fluid, this technique has proved awkward and uncertain. Closed dialysers which can be used as ultrafilters by bringing in the blood under positive hydrostatic pressure and applying negative pressure to the dialyzing fluid are most suitable for this purpose. The Skeggs-Leonards apparatus has been found clinically effective for extracellular fluid removal.[22]

Whatever their mechanical features, all systems have in common certain technical difficulties and hazards. Arterial cannulization is probably essential for adequate blood flow. Heparinization of the patient will be required, although with a minimum of moving parts and suitable nonwetting surfaces

the dose may be greatly reduced. Another potentially dangerous event can occur as a consequence of dialysis. With high rates of blood flow, hypertension gradually develops during the course of dialysis. This has sometimes been associated with a rise in cardiac output. Its occurrence with peritoneal dialysis as well suggests that there is also a humoral mechanism. Merrill and co-workers reported that 32 of 45 patients who were subjected to dialysis at blood flow rates greater than 125 ml/min. had systolic blood pressure rises of 40 mm. Hg or more.[23] There was less rise in diastolic pressure. Fortunately, this did not appear to lead to left ventricular failure. Goldner, Gordon, and Danzig[24] have been able to control the hypertension with small doses of hexamethonium.

In evaluating the clinical experience with extracorporeal dialysis we have summarized the results and general impressions of some of the most active groups working in this field, particularly Kolff, Alwall, Merrill, and their co-workers.¶ These have been supplemented by the specific experience of the Korean War, in which the artificial kidney emerged as an important aide in the management of post-traumatic renal failure.[28]

Since 1947, Alwall and his co-workers, in Sweden, have published extensively on their experiences with a stationary artificial kidney in treating both acute and chronic renal failure. Alwall has recently reported on 25 cases of "acute tubular nephritis," of which 11 were treated by physiologic methods and 14 were treated both by those measures and by dialysis.# All of the 11 physiologically treated cases survived 5 to 11 days of oliguria; 1 died in the diuretic phase as a result of myocardial infarction. Their peak nonprotein nitrogen values ranged as high as 320 mg. per 100 ml. (average, 233 mg. per 100 ml.). The course of all these patients seemed uneventful. All lost weight during oliguria. Some were given magnesium sulfate to induce diarrhea. The 14 cases treated with dialysis had oliguria for 4 to 28 days. They were older (half were over 50), and eight of them had postoperative acute renal failure, as opposed to only 2 of the 11 treated by physiological means alone. Dialysis, in this series, was usually performed because of the development of coma. Potassium intoxication occurred but was not considered a prime indication, since it was thought that glucose and insulin could adequately control this complication. Many patients had pulmonary and/or peripheral edema, but thirsting and induced diarrhea was considered adequate therapy for this, and Alwall's ultrafiltration apparatus[30] was not employed for removal of fluid. It did appear, however, that the patients with fluid excess showed an accelerated development of "uremic" symptoms. Of the 14 dialyzed cases, 1 was dialyzed on the day of diuresis and 1 was dialyzed during diuresis because of increasing "uremia." Both improved. Six of the remaining 12 recovered; 2 underwent diuresis but died of complicating ailments, and 4 died after 7, 12, 27, and 28 days of oliguria, without ever exhibiting diuresis. The age of the patients who died was 49 to 73 years (average age, 59 years).

In analyzing these cases it is apparent that older patients, especially if they develop oliguria postoperatively, do poorly. The wide variation in the rate of development of uremic symptoms remains unexplained. Alwall concludes that dialysis was often live-saving in these patients and that it should be used when "life-threatening" uremia appears, as evidenced chiefly by mental changes.

Although Swan and Merrill[31] did not present an over-all analysis of the use of dialysis in acute renal failure, the 10 cases reported by them in detail give a very similar picture to that presented by Alwall. There was a high incidence of postoperative oliguria and of complicating disorders which increased the over-all mortality. Four were dialyzed and recovered, of which one, at least, did not appear to have needed dialysis for survival. One patient recovered from oliguria after dialysis but died during diuresis, and one recovered without dialysis. Of the remaining four, two died of complicat-

¶ References 25-27.

References 13 and 29.

ing disorders during oliguria, one died of fluid excess, and one, who was dialyzed in the diuretic phase despite the presence of melena, had increased bleeding for which he required surgery and died of postoperative complications one month after his oliguric episode. The impression we have gained from these series, which has been substantiated by other reports, is that the mortality from acute tubular necrosis per se can be reduced by the combination of physiologic measures and external dialysis to nearly zero. Deaths will occur as a result of prior injudicious treatment and from associated nonrenal diseases. There will be mishaps related to heparinization if dialysis is performed in patients who manifest a bleeding potential, and these may be fatal. Merrill * does not attempt to answer the question as to whether mortality is actually reduced by dialysis except in some specific instances of potassium intoxication. Unlike Alwall, he has frequently encountered cases in which potassium intoxication occurred with physiologic methods of treatment and was the prime indication for dialysis. Merrill, however, has recommended the use of an artificial kidney in acute renal failure on the quite different grounds that it reduces morbidity and improves the patient's ability to withstand nonrenal complications. He finds that uremic symptoms may be reversed and the course of acute renal failure be made benign even in older patients with complicating disorders. These patients are ambulatory, able to eat a protein-free diet, and able to breathe and cough normally. They thus are better able to resist or avoid infection and thromboembolic complications. This approach is only valid if the procedure itself is uncomplicated.

The recent experience with renal failure following severe wounding in Korea seems to represent a special problem.[28] As noted above, the combination of multiple transfusions of old bank blood and extensive tissue destruction greatly increased the accumulation of potassium and probably also of other products of protein metabolism. Without artificial measures the mortality from acute renal failure was high. Prior to the establishment of a renal insufficiency center it was estimated at 80% to 90%. Eight of the first series of 10 patients treated by the Renal Insufficiency Center group before an artificial kidney was available died. (Their average survival was only seven days.) This mortality was reduced to 53% in 51 cases subsequently treated in the center. Of these 31 were dialyzed with 21 deaths (average survival, 12 days). Only 6 of 20 patients who did not require dialysis died. The indications for treatment were potassium intoxication and/or uremic symptoms. Repeated dialyses were often necessary, because rapid potassium accumulation and protein breakdown persisted.

If an efficient dialyzer is available, we feel that its use is safer and more comfortable than peritoneal lavage, except in those patients in whom bleeding represents a contraindication to heparinization. The development of hypertension during dialysis has not ordinarily been considered a contraindication to treating patients with acute renal failure. However, in anuria due to acute glomerulonephritis, Merrill finds that dialysis may be followed by increased hypertension and convulsions and therefore feels that the procedure should be reserved for only the most serious cases. In addition to the complications noted, errors in technique can lead to shock, pulmonary edema, or pyrogen reactions, whichever procedure is employed.

We cannot predetermine the ideal point at which to apply these measures in the treatment of acute renal failure. The decision must depend on the experience of the physicians involved. We do feel that death should not occur from reversible acute renal failure, however prolonged. Physiologic methods of therapy will carry the vast majority through the episode, and dialysis will allow the remainder sufficient time for repair of the renal lesion. Merrill's concept of employing dialysis as symptomatic therapy needs further evaluation, bearing in mind the cost of equipment and personnel. It does seem that the need for an artificial kidney as a life-saving measure

* References 27 and 32.

in acute renal failure (excluding cases resulting from battle casualties) is quite infrequent.

CONCLUDING COMMENTS

With increasing attention to correct fluid therapy, accurate cross matching of blood, and the avoidance of undue periods of hypotension, the problem of postoperative renal failure should diminish. It is postoperative patients and the seriously wounded who most often require dialytic treatment. Careful regard to the physiologic principles outlined above will suffice in most other cases of reversible acute renal shutdown to tide the patient through the period required for spontaneous recovery. The more meticulous the attention to minute detail that is given early, the less will be the need for the employment of artificial methods later.

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Case Reports

ACUTE SYSTEMIC LUPUS ERYTHEMATOSUS SYNDROME FROM HYDRALAZINE HYDROCHLORIDE

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BETWEEN April, 1953, and August, 1954, nine reports* appeared in the literature describing a variety of delayed toxic reactions which may develop in hypertensive patients who are taking hydralazine hydrochloride. It is of interest that positive L. E.-cell phenomena have been noted in six patients (Table 1) receiving this chemical.

We wish to report data concerning a patient in whom the clinical picture of acute systemic lupus erythematosus and a positive L. E.-cell phenomenon developed. This patient recovered when administration of hydralazine hydrochloride was discontinued.

A married white woman, 58 years old, has been examined periodically at the Mayo Clinic since 1942 and found to be relatively well. From 1945 until August, 1950, her blood pressure gradually increased from 160/90 to 210/100. In August, 1950, oral administration of potassium thiocyanate was begun, with satisfactory results until January, 1951, at which time a skin eruption developed, which necessitated the discontinuance of this drug. The skin eruption disappeared within the next four to six weeks.

In February, 1953, the patient's blood pressure was 200/110, and an examination of the ocular fundi showed narrowing Grade 1, focal constrictions Grade 1, and hypertensive sclerosis Grade 1 (on the basis of 1 to 4) of the retinal arterioles. At this time treatment with hydralazine hydrochloride was instituted, the initial dose being 25 mg. given orally four times each day. This dosage was gradually increased during the next few months, so that by October, 1953, the patient was taking 200 mg. four times daily. On this regimen of 200 mg. of hydralazine hydrochloride four times daily she felt well and the blood pressure was satisfactorily reduced.

TABLE 1.—*Positive L. E. Procedures in Six Patients Receiving Hydralazine Hydrochloride (Apresoline)*

Authors and Date Reported	Positive L. E. Proceedures, No.	
	Peripheral Blood	Marrow
Dustan, Taylor, Corcoran, and Page (Jan., 1954)	2	1
Perry and Schroeder (Feb., 1954)	1	..
Reinhardt and Waldron (Aug., 1954)	1	..
Shackman, Swiller, and Morrison (Aug., 1954)	1	..

Approximately one month prior to her hospital admission the patient began to note nocturnal leg cramps, fatigue, and weakness as well as edema of the feet and ankles. Shortly thereafter soreness and pain developed in the right temporomandibular joint and "canker sores" occurred in the mouth. One week prior to admission the weakness and cramping in both legs as well as the generalized fatigue became severer, and this was followed by the appearance of a tender papular skin eruption on both forearms and neck, while tender small nodules developed about the distal interphalangeal joints of both thumbs. On April 30, 1954, the patient presented herself with the foregoing complaints and findings and she was promptly admitted to the hospital. Administration of hydralazine hydrochloride was discontinued.

Physical examination revealed the patient to be quite agitated and seriously ill. Her oral temperature was 99.8 F; the heart rate was 92 beats per minute, and the blood pressure was 154/72. The above-mentioned dermatitis, present over the face, neck, forearms, and hands, consisted of discrete and confluent urticarial papules and nodules varying in

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* References 1-9.

Fig. 1.—Photographs taken April 30, 1954. (*a*) Discrete and confluent skin lesions over face, neck, and upper anterior surface of chest. (*b*) Skin lesions over forehead. (*c*) Lesion along lateral aspect of tongue.

size up to 1 cm. in diameter (Fig. 1*a*, *b*, and *c*). Several painful reddish-gray papules about 0.5 cm. in size were present in her mouth and on the lateral margins of the tongue (Fig. 1*c*). Examination of the heart, lungs, and abdomen revealed no notable abnormalities, but all distal interphalangeal joints were tender, as were the elbows. None of the peripheral joints were red or swollen, and no changes were present to suggest synovitis.

The results of laboratory studies were as follows: Urinalysis showed albuminuria Grade 1 (basis 1 to 4) and erythrocyturia Grade 1 (basis 1 to 5). Erythrocytes numbered 4,340,000, and leucocytes, 5,200 per cubic millimeter of blood, and the hemoglobin was 12.6 gm. per 100 cc. A differential leucocyte count revealed 23% lymphocytes and 77% segmented neutrophiles. Erythrocyte sedimentation rate was 77 mm. in one hour by the Westergren method. The blood Kline, Kahn, Hinton, and Wassermann reactions were negative. The blood urea

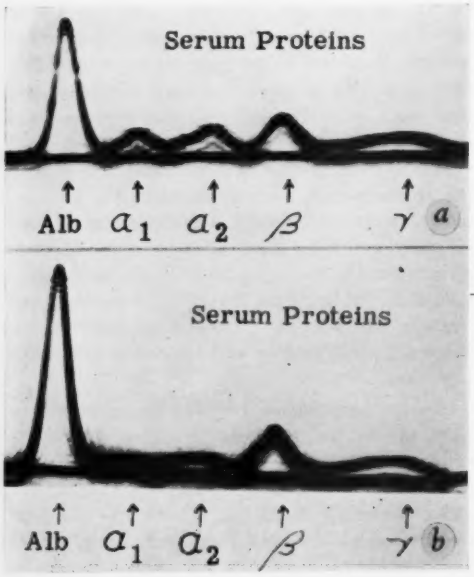

Fig. 2.—Electrophorectic patterns of serum protein.

	Normal Values, %
(*a*) May 7, 1954	
Serum albumin 40%	55.7 ± 7.9
Serum α_1-globulin 9%	5.2 ± 1.3
Serum α_2-globulin 15%	9.6 ± 2.2
Serum β-globulin 17%	14.2 ± 4.0
Serum γ-globulin 19%	15.3 ± 2.4
(*b*) Oct. 7, 1954	
Serum albumin 46%	55.7 ± 7.9
Serum α_1-globulin 7%	5.2 ± 1.3
Serum α_2-globulin 10%	9.6 ± 2.2
Serum β-globulin 20%	14.2 ± 4.0
Serum γ-globulin 17%	15.3 ± 2.4

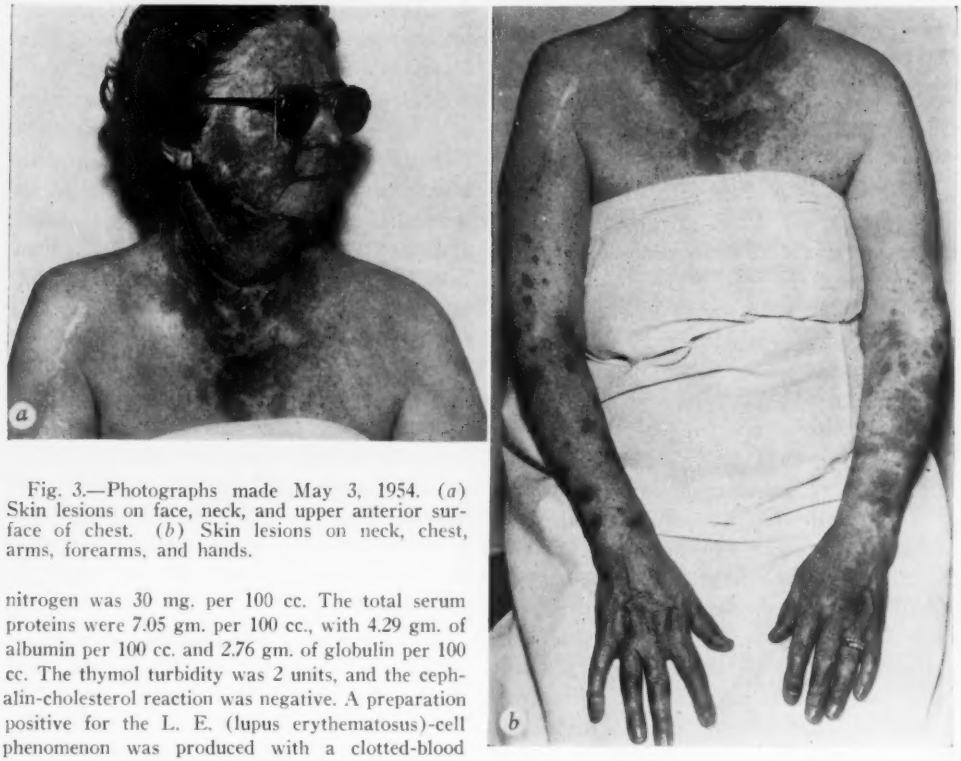

Fig. 3.—Photographs made May 3, 1954. (*a*) Skin lesions on face, neck, and upper anterior surface of chest. (*b*) Skin lesions on neck, chest, arms, forearms, and hands.

nitrogen was 30 mg. per 100 cc. The total serum proteins were 7.05 gm. per 100 cc., with 4.29 gm. of albumin per 100 cc. and 2.76 gm. of globulin per 100 cc. The thymol turbidity was 2 units, and the cephalin-cholesterol reaction was negative. A preparation positive for the L. E. (lupus erythematosus)-cell phenomenon was produced with a clotted-blood technique. Electrophorectic study † of the serum protein distribution by the Tiselius method showed a decrease of the serum albumin and an increase of the alpha and gamma globulin fractions (Fig. 2*a*).

During the first three days that the patient was in the hospital the skin rash (Fig. 3) increased in severity and spread to the trunk and legs, while the lesions in the buccal mucous membranes and on the tongue became so painful that she was unable to eat. On the 4th hospital day the skin lesions started to improve on the face and upper extremities, while by the 10th day they had all disappeared and she was again able to eat solid food. The other complaints of bodily soreness, weakness of the limbs, and generalized fatigue had also ceased. During this period of hospitalization the oral temperature ranged from 98.0 to 102.4 F. and the blood pressure varied from 110/80 to 164/100. By the 13th hospital day the patient felt so much improved that she was dismissed to her home as an outpatient. The treatment that she received while in the hospital consisted of antihistaminics, acetylsalicylic acid, and daily sedation while Schamberg's lotion was applied locally to the skin. Neither cortisone nor corticotropin was employed in treatment of this patient.

† B. F. McKenzie, Section of Biochemistry, provided these data.

It has now been nine months since this patient was dismissed from the hospital, and we have observed her closely as an outpatient during this time. Up to January, 1955, there have been no symptoms or signs to suggest recurrence of the lupus erythematosus syndrome. On Oct. 7 electrophoretic study (Tiselius) of the serum-protein distribution was again made (Fig. 2*b*). The albumin has increased about 6% but is still about 10% below normal. The globulin values are not much

TABLE 2.—*Laboratory Data*

Date, 1954	Leucocytes/ Cu. Mm.	Sedimentation Rate, Mm./Hr.	Serum L. E. Phenomenon
April 7	6,400	..	.....
30	5,200	77	.....
May 3	.....	..	Positive
5	5,700	..	.....
10	.....	110	Doubtful
19	7,000	..	.....
20	.....	95	Doubtful
26	7,900	..	.....
27	.....	89	Doubtful
June 2	4,700	..	.....
3	.....	92	Doubtful
18	.....	58	Negative
July 7	5,800	..	.....
9	.....	55	Negative
Aug. 27	4,200	39	.....
Oct. 6	.....	42	.....

above normal limits. At the same time as the electrophoretic study, the total serum protein was 6.76 gm.; the albumin, 4.52 gm., and the globulin, 2.24 gm. per 100 cc.

A summary of the leucocyte counts, erythrocyte sedimentation rates, and the L. E.-cell tests is shown in Table 2.

COMMENT

In December, 1953, Morrow and co-workers [1] reported their observations on the use of hydralazine hydrochloride and hexamethonium in 258 hypertensive patients treated over a period of 6 to 25 months. Arthritis and "collagen-like disease" were noted in 16 patients. No positive L. E.-cell phenomena were reported.

In January, 1954, Dustan and associates [2] summarized their observations on 13 of 139 patients whose only hypertensive therapy was hydralazine hydrochloride. Eight of these patients had reactions similar to rheumatoid arthritis, and five had a more severe febrile illness. Of these five, one patient had a positive plasma L. E.-cell reaction, and in another L. E. cells were noted in the bone marrow (Table 1). It is to be noted also that these authors found a positive plasma L. E.-cell reaction in a patient who was receiving hydralazine hydrochloride and yet who did not have any signs or symptoms of lupus erythematosus.

Perry and Schroeder [3] summarized their further experiences with 17 of 211 hypertensive patients receiving hydralazine hydrochloride and hexamethonium in whom collagen disease of varying degrees of severity appeared to develop. A positive plasma L. E.-cell reaction was reported in one of these patients, though two others displayed a clinical picture difficult to distinguish from a disseminated lupus erythematosus.

Further reports by Harris and Turner,[4] Slonim,[5] Reinhardt and Waldron,[6] and Shackman and co-workers [7] served to emphasize that hydralazine hydrochloride seemed to be producing toxic reactions in some hypertensive patients. The last two reports ‡ each concerned single patients in whom the clinical picture of acute lupus erythematosus developed, and in each a positive L. E.-cell phenomenon was induced in the peripheral blood.

The side-effects of hydralazine hydrochloride may appear rapidly or may be delayed for several months. The immediate effects are well known; some of these are headache, coryza, fever, fatigue, palpitation, and angina pectoris. The delayed reactions have appeared after 2 to 22 months of continued hydralazine hydrochloride administration and take the form of "collagen disease" in all degrees of severity. The mildest is arthralgia, and the most severe are like acute rheumatoid arthritis and acute systemic lupus erythematosus. In most instances, these reactions spontaneously subside when administration of hydralazine hydrochloride is discontinued. Several patients have received cortisone or corticotropin (ACTH) with symptomatic relief.[2]

It is interesting to note that in nearly all patients in whom serious delayed reactions develop the blood pressures seem to be at normal or near normal levels § during the reaction.

Many kinds of laboratory tests have been done on patients in whom these serious delayed reactions to hydralazine hydrochloride developed. Some of the abnormalities which have been reported are erythrocyturia, albuminuria, microcytic or normocytic anemia, leucopenia, and elevation of the erythrocyte sedimentation rate. Other special studies have revealed abnormal results of cephalin-cholesterol and thymol-turbidity tests, elevated serum polysaccharides, and hyperglobulinemia. Changes in the serum protein distribution as measured by the Tiselius method of electrophoresis consist of a decrease of serum albumin and an increase of the alpha and gamma globulins.

This patient's illness was similar to those which have been previously reported to occur following prolonged use of this drug, and she rapidly recovered when administration of hydralazine hydrochloride was discontinued. This syndrome in our patient ap-

‡ References 6 and 7.

§ References 2 and 3.

peared 14 months after administration of hydralazine hydrochloride was begun. The initial dose was 25 mg. four times daily, and this was gradually increased so that in eight months she was taking 200 mg. four times daily for a total dose of 800 mg. per day, and she took this amount until the severe reaction appeared. In October, 1951, the patient's blood pressure was recorded on one occasion to be 210/100. In February, 1953, when she was taking aminophylline and phenobarbital and prior to the administration of hydralazine hydrochloride, a blood pressure determination was 200/100. While the patient was taking 800 mg. of hydralazine hydrochloride daily and during the acute systemic lupus-erythematosus-like reaction her blood pressure was at normal or near normal levels. On May 26, 1954, her blood pressure was 170/90. On June 2 her blood pressure was 170/100, and at this time she started taking a preparation of Rauwolfia serpentina. In July, 1954, an examination of the ocular fundi showed Grade 1 generalized narrowing and Grade 1 to 2 hypertensive scelrosis of the retinal arterioles. On Oct. 6 her blood pressure was 190/90. Between June 2 and Oct. 6 the blood pressure readings ranged from a high of 180/90 to a low of 150/80.

There was no clearly defined history of previous allergic disorders except that at one time a skin rash developed while she was taking potassium thiocyanate.

It is to be noted that one month before admission to the hospital pedal edema, fatigue, generalized weakness, and cramping in both calves developed, and one would suspect that this was the time of onset of the drug reaction. We did not see the patient at this time, however, and she continued to take hydralazine hydrochloride. The administration of hydralazine hydrochloride should have been discontinued at this time. It is apparent that the severity of the reaction increased one week prior to admission; for she then had pain in a temporomandibular joint, painful lesions on her tongue, more weakness, a skin rash on both forearms, and then painful nodules on the distal interphalangeal thumb joints, which were probably rheumatoid nodules. Biopsy of a subcutaneous nodule in a patient with the acute lupus erythematosus reaction from hydralazine hydrochloride has been reported by Reinhardt and Waldron.[6] These same authors also reported that biopsy of a facial lesion showed acute collagenous necrosis.

Whether these delayed reactions from prolonged use of hydralazine hydrochloride are a manifestation of hypersensitivity or are due to some other mechanism is as yet unknown.

One seems justified in stating that hydralazine hydrochloride can produce in some persons a syndrome simulating acute systemic lupus erythematosus. There are some minor differences between this type of delayed-reaction syndrome and the disease entity which seems to appear spontaneously and which is called "acute systemic lupus erythematosus." On the other hand, this reaction syndrome from hydralazine hydrochloride and acute lupus erythematosus may be one and the same thing, and there is considerable evidence to support such a view. It is conceivable that several agents can act as antigens and produce systemic lupus erythematosus and if the known agent can be withdrawn the abnormal reaction in the body is reversible. It would seem to us that our patient had acute systemic lupus erythematosus and that she promptly recovered when hydralazine hydrochloride was withdrawn.

One might wonder whether the patients in whom this severe reaction has developed might have had latent lupus erythematosus which was "unmasked" by hydralazine hydrochloride. It is of considerable interest that Dustan and associates found a positive L. E.-cell phenomenon in the peripheral blood of a patient who was taking hydralazine hydrochloride and yet this patient did not have any signs or symptoms of the disease. Considering what has been stated so far, it might seem advisable to do L. E.-cell tests on all patients before hydralazine hydrochloride is administered for the first time and to do L. E.-cell tests periodically while the patient is taking the drug even though

all seems to be going well. It will be of interest to observe the future progress of this group of patients in whom these severe delayed reactions have developed. This agent will continue to be used in the present treatment for hypertension until further experience and knowledge of hydralazine hydrochloride establish its comparative worth among the antihypertensive agents.

SUMMARY

Details pertaining to the development of acute systemic lupus erythematosus or a syndrome simulating that disease during prolonged therapy with hydralazine hydrochloride have been presented. A positive L. E.-cell phenomenon was observed. The patient recovered and the L. E.-cell phenomenon disappeared when the hydralazine hydrochloride was withdrawn.

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LEUCOAGGLUTININS IN AGRANULOCYTOSIS

Report of a Case

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and
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An immunologic mechanism has long been suspected as a key factor in the pathogenesis of certain types of agranulocytosis as well as in syndromes characterized by a paucity of either erythrocytes or platelets. It has been only in the last few years, however, that techniques for the demonstration of blood cell sensitivity phenomena have been developed. Thus, coating antibodies have been discovered in acquired hemolytic anemia, and platelet agglutinins have been demonstrated, at times in exceedingly high titers, in idiopathic thrombocytopenic purpura.* Recently, European workers have reported white blood cell agglutinins in neutropenia and diverse techniques for their in vitro demonstration.†

We have lately observed over a period of many months a patient with idiopathic agranulocytosis in whom white blood cell agglutinins were repeatedly demonstrated. This is, we believe, the first reported case of this type to be presented with autopsy findings.

REPORT OF CASE

First Admission.—The patient (M. H. 64889), a 55-year-old white woman, was admitted in January, 1954, complaining of a lump in her left breast noted one month prior to admission. Increasing "weakness" had characterized the previous six months. During that time she had lost 6 lb. (2.7 kg.). There was a past history of bilateral cataract extraction.

Physical examination revealed only aphakia and a firm solitary nontender mass in the left breast. Routine blood cell counts (Fig. 1), a fasting blood sugar determination, and a blood urea nitrogen determination were within normal limits.

On Jan. 8, 1954, left radical mastectomy was performed. A 4 cm. mass diagnosed as anaplastic carcinoma of breast was found. There were axillary metastases. Preoperatively and postoperatively the patient received three units of 500 ml. each of compatible blood, crystalline penicillin G procaine (Crysticillin), secobarbital (Seconal), codeine, and acetylsalicylic acid.

She made an uneventful recovery, and on March 24, 1954, after the mastectomy wound had healed, a course of radiotherapy was begun. By April 23, 1954, she had received a total of 1,800 r both to left anterior chest and supraclavicular area and to the left posterior axilla. At this time a white cell count of 2,400 forced cessation of radiotherapy. Leucopenia persisted through May and June (Fig. 1). A right iliac bone marrow aspiration taken in May revealed "severe generalized hypoplasia." In spite of her blood picture the patient remained asymptomatic.

Second Admission.—The patient was readmitted for hematologic study on July 9, 1954. She complained only of "weakness." Careful questioning elicited no history of ingestion of medications. Physical examination revealed an afebrile comfortable well-nourished woman. There was no evidence of hepatosplenomegaly, lymphadenopathy, pallor, petechiae, ecchymoses, or mouth lesions. Moderate lymphedema of the left arm was noted.

Blood cell counts are summarized in Fig. 1. Platelet counts ranged from 160,000 to 330,000 per cu. mm. Reticulocyte counts ranged between 0.2% and 1.9%. Red cell agglutinins could be demonstrated neither by the direct and indirect Coombs test nor by the use of trypsin-treated cells. Epinephrine injection failed to precipitate a leucocytosis. An L. E. cell test employing compatible donor white cells was negative. A leucoagglutinin, as described below, was repeatedly demonstrated. Fasting blood sugar, serum inorganic phosphorus, alkaline phosphatase, serum calcium, and serum bilirubin values were within normal limits. Blood uric acid was 2.2 mg. per 100 cc. Total serum protein was 6.4 gm.; albumin was 4.4 gm., and globulin was 2 gm. per

From the Division of Neoplastic Diseases, Montefiore Hospital.

* References 1-6.

† References 7-9.

100 cc. Paper electrophoretic analysis of serum proteins demonstrated an alpha-two peak. Gamma globulins were present in normal concentrations. Identical curves were obtained using fresh serum and serum stored at —15 C for three weeks. An x-ray bone survey revealed no evidence of metastases.

Three sternal bone marrow aspirations were performed. On July 28, 1954, a hypoplastic specimen was received. The myeloid-erythroid ratio was normal. A large number of blast forms was present, representing 50% of the total leucocyte population. These blast forms most closely resembled myeloblasts. Megakaryocytes were reduced in number. On Aug. 25, 1954, a fatty, hypoplastic specimen was obtained. Megakaryocytes were normal. The myeloid series was grossly abnormal. Early myelocytes predominated. There were a few myeloblasts and very few adult polymorphonuclear leucocytes. On Sept. 27, 1954, a markedly hyperplastic marrow was obtained. Megakaryocytes were diminished in number, but platelets appeared normal. Marked myeloid hyperplasia was present. The myeloid-erythroid ratio was 10:1. Eighty per cent of the cells of the myeloid series were myelocytes. Fifteen per cent were blasts. There were very few young neutrophiles. No tumor cells were seen. A biopsy of the left iliac crest did not reveal tumor cells.

On admission the patient was given tetracycline (Achromycin) as a prophylactic measure. Cortisone therapy was begun in an effort to induce a polymorphonuclear leucocytosis. Later, testosterone was added to the regimen. In spite of therapy the clinical condition remained unchanged until two months after admission, when the patient developed a monilial and mixed bacterial pharyngitis. Erythromycin, fungicidin (mycostatin), and local gentian violet succeeded in reducing the fever and in partially relieving the pharyngitis. Hoarseness and a nonproductive cough, however, remained. On Oct. 26, 1954, epigastric distress and a generalized maculopapular rash were noted. Thereafter, the clinical course was progressively downhill. Spiking fever persisted in spite of intensive antibiotic therapy. Diarrhea, bilateral basilar pneumonitis, and coma preceded her death, three weeks later. Terminally her temperature rose to 105 F. At no time did hepatosplenomegaly or a bleeding tendency develop.

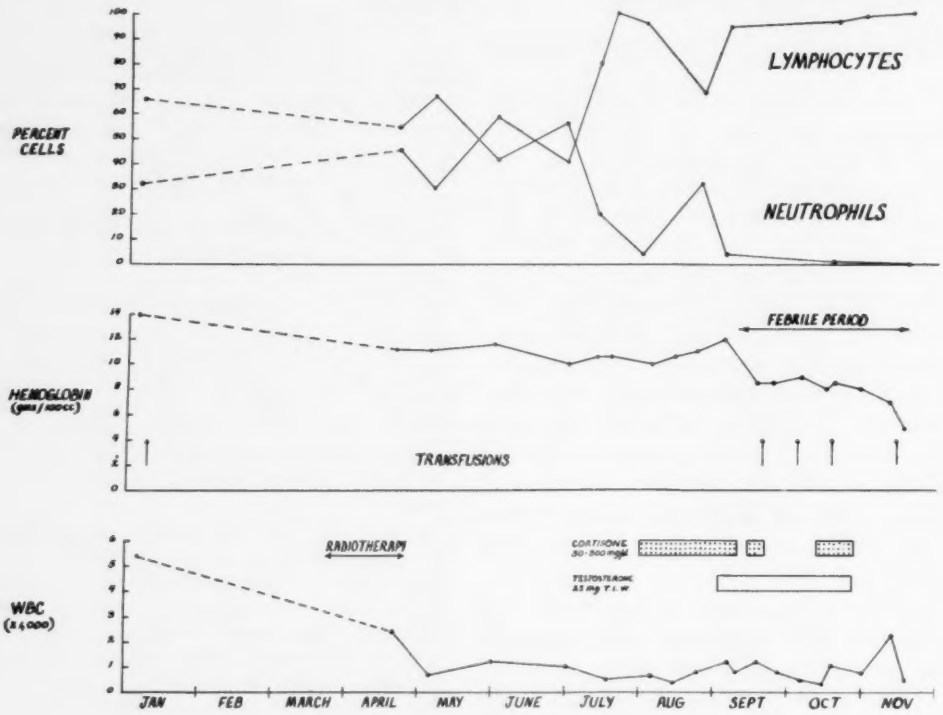


Fig. 1.—Hematologic course of patient.

Autopsy was performed approximately two hours after death. Jaundice, edema, cyanosis, clubbing, and peripheral adenopathy were absent. Irregular punched-out pharyngeal ulcers with surface slough

were noted. A few tiny cervical nodes were found. Pleural surfaces were covered with a fine fibrinous exudate. On cut section the lungs were characterized by a dark red parenchyma in which a few dark hemorrhagic areas were scattered. In the left lower lobe a 2 cm. nodule of gray-white tissue was found. Hilar nodes were not enlarged.

The liver weighed 1,750 gm. It was grossly normal. The spleen weighed 200 gm. It was of normal shape, size, and consistency. On cut section it exhibited only moderate congestion. The esophagus throughout its whole length was deeply ulcerated. The cecum and proximal four inches of colon were also studded with areas of ulceration. The bladder wall was thin. Areas of bladder mucosa were hemorrhagic.

Bone from sternum, ribs, vertebral column, and iliac crest was examined. Bony architecture appeared normal. Marrow was purple.

On microscopic examination bone marrow sections were moderately cellular but not hyperplastic. There was some degree of erythroid hyperplasia. White blood cell elements predominated. These exhibited a marked left shift, with a predominance of early forms up to and including metamyelocytes. A large number of scattered plasma cells was present. The over-all picture was that of a maturation arrest of the myeloid series.

The lung exhibited focal areas of atelectasis and areas of severe congestion and hemorrhage. The alveoli were packed with erythrocytes. Patchy areas of inflammation were characterized by collections of large macrophages, lymphocytes, and plasma cells. No neutrophiles were seen. Focal collections of Gram-negative bacteria were seen throughout. The nodular lesion described grossly was a monilial granuloma.

The ulcerations of the pharynx, epiglottis, esophagus, cecum, and colon demonstrated a heavy growth of monilial hyphae, bacterial colonies, and a cellular exudate of the type found in the lung.

The lymph nodes were somewhat hyperplastic but not enlarged. Some of the nodes were hemorrhagic and contained large numbers of plasma cells.

The spleen was congested. Germinal follicles were small. Large numbers of plasma cells were seen. Hemosiderosis was present. Large clumps of bacteria were scattered throughout sections examined. There was no polymorphonuclear reaction. Liver, heart, pancreas, adrenal, kidneys, thyroid, and parathyroid glands were normal.

Sections of the right breast showed normal involutional changes. There was no evidence of carcinoma in these or in any of the sections previously described.

Examination of the brain was performed. There was no evidence of inflammatory or neoplastic disease.

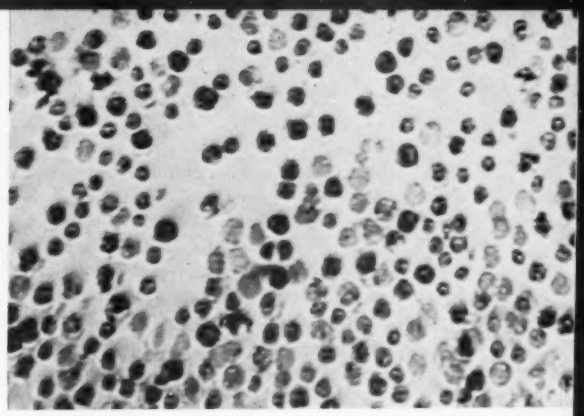


Fig. 2.—Negative leucoagglutinin test. White blood cells are dispersed throughout the field.

The anatomic diagnoses were agranulocytic angina with ulceration of pharynx, epiglottis, larynx, cecum, and proximal colon; caseous monilial granuloma of left lower lobe of lung; monilial ulcerations of epiglottis, pharynx, and esophagus.

EXPERIMENTAL STUDIES

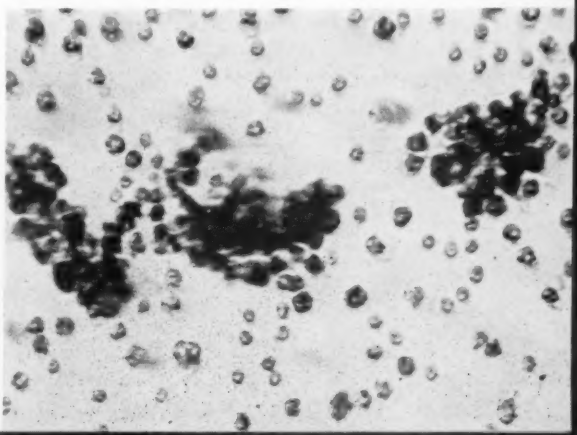
Test Serum.—Fresh sera, sera stored at —15 C, and sera stored at 4 C for one to three days were used. Before incubation, the serum was heated at 56 C for one-half hour, to remove the inhibiting factor described by Dausset.[8] It was found that leucoagglutination occurred in all storage forms mentioned, as well as in frozen stored, unheated serum. However, maximum agglutination occurred in heated serum, whether fresh or previously stored.

Control Sera.—More than 20 control sera were used. These included specimens from patients with various disorders including leukemia, malignant disease, neurologic diseases, and tuberculosis. One sample from a patient with quinidine purpura was tested. None of the control sera agglutinated white cells. Antileucocytic serum prepared in rabbits was used as a positive control.‡

Preparation of White Cell Suspensions.—Dausset's method was utilized. Twenty-five milliliters of blood was shaken in an Erlenmeyer flask containing 10 small glass balls. The resulting defibrinated blood

‡ Courtesy of Dr. Robert Slater, Department of Pediatrics, New York Hospital, New York.

Fig. 3.—Strongly positive leucoagglutinin reaction. Donor white cells incubated with patient's serum.



was decanted from the clot. To this blood one-fifth volume of high-molecular-weight Dextran was added.§ The mixture was allowed to settle in a water bath at 37 C. The supernatant was pipetted off and stored for a short period at 4 C until it was required for the test procedure. Donor cells from numerous compatible bloods were used.

Test Procedure.—To 0.2 ml. of test serum was added 0.1 ml. of white cell suspension. The mixture was allowed to incubate at 37 C for one hour. At the end of the hour the tubes were agitated for five minutes to prevent spontaneous clumping. Two drops of 2% acetic acid were then added to the mixture. One drop of the suspension was next placed on a glass slide and examined under the microscope at various magnifications. A negative test (Fig. 2) was characterized by uniform dispersion of white cells throughout the microscopic fields. Positive tests were graded 1+ to 4+ on the basis of number and size of white cell aggregates (Fig. 3). When observed under oil, the finer structure of the agglutinated cells was seen to be intact.

Many modifications of technique were used. It was found that agglutination was not appreciably inhibited by the use of siliconized glassware. Sterile technique was utilized in one series of experiments. This did not alter results described above. The use of heparin produced unreadable microsocpic fields. Saponin effectively lysed red cells and spared white cells; however, it caused clumping in all tubes.

COMMENT

During the 1930's many cases of agranulocytosis were observed.|| The causative role of certain drugs, especially aminopyrine, was noted. A neutropenic response, however, appeared only in certain persons. In these patients the neutropenia was frequently fulminant. Where aminopyrine was the causative agent, it might have followed the ingestion of very small amounts of the drug. Chills, fever, and malaise would frequently precede the onset of agranulocytosis.

This clinical picture suggested to some an underlying sensitivity phenomenon.¶ Their impressions were reinforced in 1936 by the work of Dameshek and Colmes.[13] These investigators produced local wheal and flare reactions and rapid depression of white cell count in sensitive persons by intradermal injection of a mixture of aminopyrine and blood serum. In spite of this work little more was done to characterize this reaction. Indeed, only seven years ago Hickie noted:

> A search of the extensive literature about agranulocytosis in the past twenty five years has revealed only three references to investigation of the effect of the affected patient's serum on normal leukocytes, and none of these was very informative.[14]

Attention instead had focused upon the immunology of red cells and platelets.# A significant contribution was made by Stefanini and co-workers, who studied a patient with idiopathic thrombocytopenic purpura.[6] Serum from this patient contained high titers of in vitro platelet agglutinins. Injection of this serum into normal persons induced a marked peripheral thrombocytopenia and a striking increase in numbers of immature megakaryocytes in their bone marrows. This bone marrow alteration is analagous to that described for white cells by Fitz-Hugh and Krumbhaar, who were the first to point out that the bone marrow of agranulocytosis is characterized by arrested maturation of the myeloid series.[15]

To date, however, no such shift to the left has been demonstrated in normal marrows secondary to the injection of serum containing leucoagglutinins. Nevertheless, several workers have demonstrated in vitro white cell agglutinins and their neutropenic effects subsequent to injection into normal persons. Thus, at about the same time that Stefanini's group reported on platelet agglutinins, Moeschlin and Wagner demonstrated a leucopenia in two normal persons occurring within 20 to 40 minutes after transfusion of blood from an aminopyrine-sensitive patient.[7] In vitro agglutination of autologous and homologous leucocytes was also exhibited by the serum of the aminopyrine-sensitive patient. Other workers have induced neutropenia in normal persons by the transfusion of whole blood from patients with leucopenias apparently unrelated to drug ingestion.[16]

Martensson and Vikbladh reported a patient whose leucoagglutinin titer fell with cortisone therapy. This patient complained

§ Courtesy of Dr. Lee Burnett, Lenox Hill Hospital, New York.

|| References 10 and 11.

¶ References 11 and 12.

References 1-6.

of joint pains and fever. Neutropenia and elevated serum globulins were noted on blood examination.[9] Moeschlin and co-workers demonstrated white cell agglutinins in the serum of a patient with primary atypical pneumonia and pancytopenia. Serum globulins were not elevated in this case.[18]

The most extensive studies have been reported by Dausset, who has described in vitro leucoagglutinins in the sera of 39 patients with neutropenia and in 9 patients with normal white cell counts. All patients in his series had received multiple transfusions.[17]

Dausset and his group characterize the leucoagglutinin as a thermostable substance, probably a gamma globulin, reacting optimally at 37 C.[8] It is preserved by freezing, unaffected by shifts of pH between 6.5 and 9.2, and destroyed by heating at 65 C for 30 minutes. It acts on both normal and pathologic granulocytes and lymphocytes. No agglutination of the patient's white cells, however, could be demonstrated by his own serum. The agglutination reaction did not fix complement. It was inhibited by a thermolabile substance in serum.

A survey of these reports indicates that various techniques have been used to demonstrate in vitro leucoagglutination. Dausset used defibrinated blood, water-wettable surfaces, nonsterile technique, and high-molecular-weight sedimenting agents. He heated the test serum to destroy an inhibiting factor, which is not complement. He noted that the use of heparin caused false positive reactions. Martensson and Vikbladh used siliconized apparatus, heparinized blood, unheated test serum, and water-wettable surfaces. Moeschlin used water-wettable surfaces, heparinized blood, and unheated test serum.

We have found that agglutination in the case presented proceeded with or without the employment of sterile technique and with or without the use of siliconized apparatus. Frozen, stored, unheated serum produced white cell agglutination, but heating the serum at 56 C for one-half hour intensified agglutination. Results with heparin were unsatisfactory. Further studies are in progress.

It is evident that, regardless of varying techniques for their demonstration, substances occur in the serum of certain patients with neutropenia which agglutinate white cells. Though their role in the pathogenesis of this condition has yet to be fully defined, we suggest that leucoagglutinins play an important role peripherally and perhaps at the bone marrow level in the production of neutropenia and maturation arrest. Their demonstration unlocks a door long closed and provides a tool for further research.

SUMMARY

A case of agranulocytic angina in which a leucoagglutinin was repeatedly demonstrated is reported.

In vitro methods for the demonstration of leucoagglutinins are discussed.

The possible role of white cell agglutinins in the pathogenesis of agranulocytosis is considered.

Dr. Daphne Granger performed the postmortem examination, and Dr. Harry M. Zimmerman, Chief of the Laboratory Division, correlated the pathologic data. Dr. John Gruhn gave time and the use of equipment. Dr. Daniel Laszlo, Chief of the Division of Neoplastic Diseases, gave encouragement and suggestions.

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PAGET'S DISEASE (OSTEITIS DEFORMANS) FOLLOWED FOR TWENTY-ONE YEARS

Report of a Case

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THE CASE briefly reported here has been under our observation for 21 years, thus offering an opportunity to make long-term observations, especially on the rate of enlargement of the head circumference and on the alkaline phosphatase blood levels. A summary of our present knowledge of osteitis deformans is worth restating, and it is briefly as follows.

REVIEW OF OSTEITIS DEFORMANS

Osteitis deformans * is more important in the differential diagnosis of musculoskeletal disorders than is usually recognized. It commonly causes deformity in one or more of the long bones, and, as a result of the deranged body mechanics, may result in joint pain and disability simulating some forms of arthritis. The pathology may also involve the joint structures themselves. The hip joint, directly or indirectly, is the one most commonly involved. In spite of these clinical manifestations, and probably because the disease starts so insidiously, the diagnosis is often made accidentally, in the course of x-ray examinations for unrelated conditions.

The incidence is greater than is commonly thought. Schmorl found it present at autopsy in 3% of persons over 40 years of age. This would make it almost as important as some of the more frequently discussed disorders, such as gout. Statistics are difficult to obtain, however, as it is now recognized that a great deal of Paget's disease is symptomless. Gutman and Kasabash, in a thorough report in 1936,[4] found 59 cases among 200,000 patients in one clinic and hospital discharge study. Seventy per cent of these were over 30 years of age. The clinically recognized cases are obviously only a small proportion of the actual incidence. Sex, nationality, and occupation are not factors. At times two or more members of one family may be afflicted.

Types.—There appears to be only one type of Paget's disease. The impression that those cases with and those without skull involvement are different types is probably due only to the striking facies and body mechanics presented by those cases with skull involvement. The disorder is a localized rather than a constitutional or generalized disease of bone, but it usually involves more than one bone, the so-called monostatic type being rare. Almost any bone or combination of bones may be involved.

Diagnosis.—X-ray [5] is essential, except in the clinically advanced forms, those with marked bowing of one or more extremity, and those with enlarged calvariums. Well over half of the cases have no clinical evidence. The skull, of course, should always be x-rayed in suspected cases. Confusion with some forms of metastatic bone involvement may occur. Case E. B. (Figure 1) illustrates this well. Backache induced us to x-ray the spine, which showed osteoblastic changes of the entire body of the second lumbar vertebra. This was interpreted as a metatastic involvement until x-ray of all the bones of the body showed only this lesion and the characteristic skull changes.

Presented before the New York Rheumatism Association, New York, Jan. 12, 1955.

From the Arthritis Clinic, University Hospital, and Bellevue Hospital Fourth Division; Associate Professor of Clinical Medicine, New York University Post Graduate Medical School.

* References 1-3.

The serum always shows an elevation of the alkaline phosphatase level,[6] and the degree of variation from normal is considered a gauge of the activity of the disease, as alkaline phosphatase is considered an index of osteoblastic bone formation.† It is not, of course, specific for Paget's disease, as other conditions, such as some metastatic bone involvement and some liver disorders, will show an elevation. The erythrocyte sedimentation rate is usually accelerated. The calcium and phosphorus blood levels are normal.

Complications. — Osteoarthritis of a marked degree is common in Paget's disease. This may be presupposed, since the derangement of body mechanics puts undue stress on the cartilages and other articular structures of involved and adjacent joints. Arteriosclerosis has been thought to be more marked than in normal subjects, but this is questionable. The diagnosis is usually made between the ages of 40 and 60. Bone sarcoma has been considered commoner in osteitis deformans ever since the classic case of Sir James Paget exhibited this complication. However, we ourselves have never seen a case, and Gutman and Kasabach found none in their large series. Impaired hearing is very common, due to pressure of the enlarging calvarium on the auditory nerve.

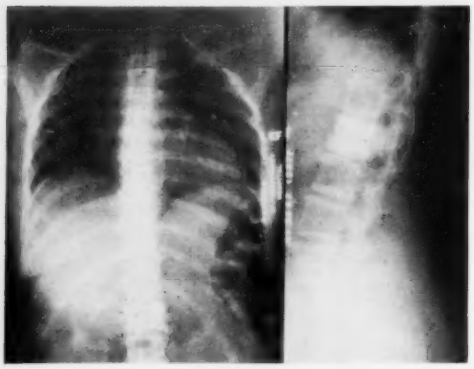

Fig. 1 (Case E. B.).—Sclerotic changes in the body of the first lumbar vertebra. The skull showed the characteristic changes of Paget's disease.

Fractures appear to be more frequent than in normal subjects. Incomplete linear spontaneous fractures can be seen by x-ray in most subjects and probably make the bones more susceptible to minimal traumas. The bone deformity may tax the ingenuity of the surgeon when he applies the fracture apparatus. However, the fractures heal normally and in some cases appear to heal faster than the average.

Etiology.—The cause of osteitis deformans is still unknown. It is obviously a localized bone disease, as only parts of bones are involved, and many bones are completely normal. Paget's original suggestion that the disease is an inflammation is not tenable, the heat and redness being due to increased vascularity of the lesions. There are no local or general signs of inflammation. Arteriosclerosis with nutritional impairment is not tenable either. Endocrine derangements have been suggested without adequate proof.

Pathology.—No new observations have been added in recent years. (See especially Schmorl[9] and Jaffe.[10])

Treatment.—Treatment in our cases, as well as the treatment recommended by most clinics, has been limited to the administration of measures which promote calcium intake and absorption and bone formation. These include a high-calcium high-protein low-fat diet, vitamin D, and estrogens and androgens, all with equivocal effect. X-ray therapy helps to control pain when it is present, but it has not affected the course of the disease. Orthopedic measures to offset the body mechanical derangements are important. Corrective exercises to militate against impairment of joint function and sequential osteoarthritis should always be included in the management.

REPORT OF CASE

C. L., a white man, first noticed painless deformity of the right tibia in 1933, at the age of 54. By this time the disorder was well advanced, roentgenograms of the skull showing extensive involvement. As in many cases of osteitis fibrosa, the extent of the deformity, before this intelligent patient became aware of it, was hardly credible. An outline men-

† References 7 and 8.

tioning some of the major landmarks in the history is as follows:

Year born	1879	
Bowing of right leg pointed out by wife in	1933	Age 54
Under our management since	1933	Age 54
Hearing became noticeably defective in	1946	Age 67
Fracture of right humerus; repair faster than average; no evidence of bone tumor	1947	Age 68
Duodenal ulcer with hemorrhage; satisfactory recovery	1951	Age 72
Left maxilla extensively involved; discharging sinus formed, bone spicules extruded, on section characteristic of osteitis deformans	1953	Age 74
Fracture of right femur	1954	Age 75

All pertinent laboratory tests were normal except for the alkaline phosphatase determinations. These studies are summarized in Table 1. The sedimentation rate was usually moderately elevated.

TABLE 1.—*Alkaline Phosphatase Values*

Date	Bodansky Units	Date	Bodansky Units
5/31/33	65.1	10/17/45	28.5
8/ 4/33	25.		
		4/24/46	32.6
1/ 2/34	61.	6/12/46	27.7
9/18/34	59.1		
12/20/34	72.	2/ 5/47	44.4
		4/30/47	38.7
6/ 6/35	9.2	9/ 3/47	31.0
		11/26/47	48.2
3/26/37	26.		
10/26/38	58.3		
10/26/38	58.3	2/25/48	45.8
		4/22/48	17.1
10/26/38	35.0	6/10/48	36.6
5/10/39	25.4	9/15/48	35.4
9/20/39	21.0	12/15/48	46.6
4/24/40	26.1		
6/12/40	29.2	12/16/49	30.7
7/31/40	11.4	5/16/49	45.2
		8/30/49	19.7
4/16/41	34.2		
7/ 2/41	18.3	1/ 3/50	43.9
10/ 4/41	28.0	4/ 7/50	38.2
		12/ 8/50	22.3
4/15/42	26.1		
4/ 7/42	17.0	4/19/51	32.0
5/ 7/43	....	6/ 4/51	25.2
5/26/43	....	11/25/51	34.6
9/22/43	25.6		
9/27/43	28.3	9/22/52	22.7
2/ 3/44	12.0	12/ 3/54	38.3
8/ 2/44	28.8	12/10/54	48.5

TABLE 2.—*Maximum Skull Measurements*

Date	Circumference, Cm.
5/26/33 (age 53)	57.5
7/10/35	58.2
3/23/41	60.5
4/12/41	60.5
5/14/41	60.5
7/16/41	60.5
1/ 4/43	60.6
2/14/45	61.5
8/17/45	61.5
6/19/46	62.0
3/ 3/48	62.8
6/17/48	62.8
9/22/48	63.0
6/ 8/49	63.2
9/15/50	63.5
10/ 3/51	64.0
1/18/52	64.0
7/.../54	64.5
11/23/54	64.5

The skull, which showed the classic cotton-wool effect at the first x-ray examination, only very gradually exhibited progression of these changes. The circumference of the skull increased as recorded in Table 2.

Fig. 2, superimposing the data for the alkaline phosphatase determinations and the head circumference, shows that the circumference of the head gradually and more or less uniformly increased, whereas the alkaline phosphatase exhibited extreme variations. These variations could not be correlated with any clinical manifestations in the history or in the physical examination.

If the skull volume above the circumference measured may be imagined as half of a perfect sphere, then we can calculate its volume as equal to $\frac{\pi D^3}{6}$ divided by two. Calculating this figure for each of the circumference measurements taken gives us results which show that the skull volume is increasing at a faster rate than is the circumference and that this is occurring at an accelerated rate as the years pass.

The management outlined above was instituted and has been persisted in to date, but the effect on the course of the disease has been impossible to determine. The progression has been extremely slow but persistent.

SUMMARY

A case of osteitis deformans (Paget's disease) is presented, with continuous observations from 1933 to date, showing (1) a gradual progression of the disease in spite of the therapy, (2) alkaline phosphatase studies, done periodically over 21 years,

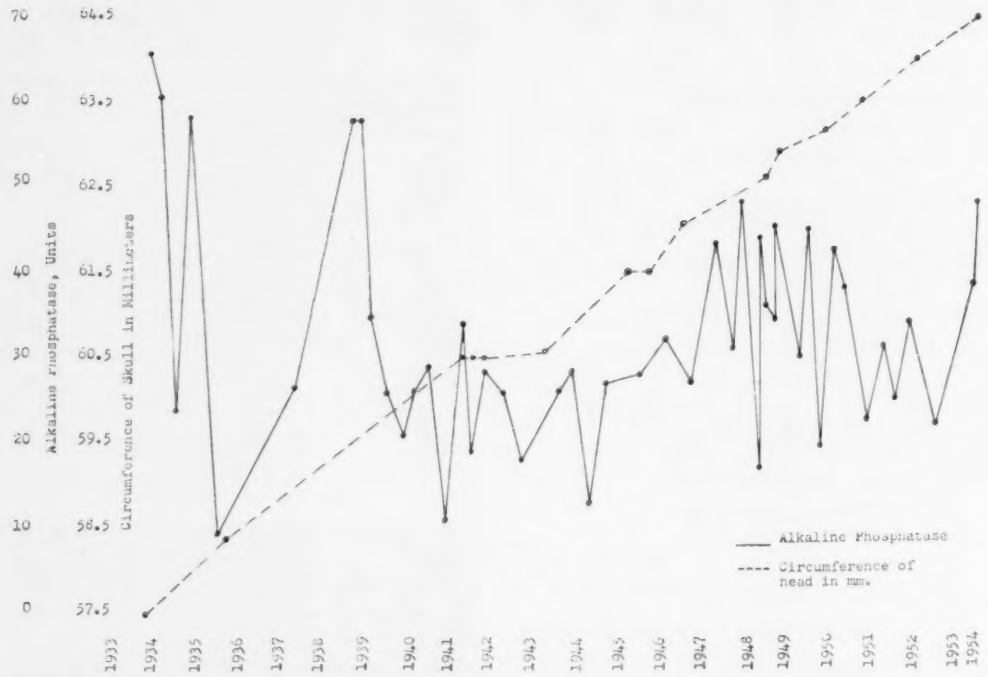

Fig. 2.—Alkaline phosphatase blood levels and circumference of head from years 1933 to 1954.

which exhibit considerable variation without any perceptible association with the clinical course, and (3) a steady uniform increase in the head circumference through the years.

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News and Comment

ANNOUNCEMENTS

Postgraduate Assembly in Endocrinology and Metabolism.—The Seventh Postgraduate Assembly in Endocrinology and Metabolism, sponsored jointly by the Endocrine Society and the Indiana University School of Medicine at the Indiana University Medical Center, Indianapolis, will be held Sept. 26 to Oct. 1, 1955.

The faculty will consist of twenty-one eminent clinicians and investigators from various parts of the country in the fields of endocrinology and metabolism. The program will cover the various endocrinopathies, with emphasis on the clinical aspects, demonstration of laboratory tests, presentations of cases, and question-and-answer panel discussions. The course is designed to cover the main aspects of diagnosis and therapy in the field of endocrinology and metabolism for the physician in general practice and for those in other specialties who wish to have a general knowledge of this rapidly growing field.

A syllabus with brief abstracts of lectures will be available to the registrants at the time of the assembly.

For further information concerning the program, write Post Graduate Office, Indiana University Medical Center, 1100 W. Michigan St., Indianapolis 7. Registration is limited to 100; tuition fee is $100.00. Arrangements for housing accommodations will be made through the University.

Laboratory Refresher Training Courses.—The Department of Health, Education, and Welfare announces a series of Laboratory Refresher Training Courses to be given by the Laboratory Branch of the Communicable Disease Center during the period September, 1955, to April, 1956.

Information and application forms should be requested from Laboratory Training Services, Communicable Disease Center, U. S. Public Health Service, P. O. Box 185, Chamblee, Ga.

CORRECTION

In the article "Syphilis: Review of the Recent Literature," by Dr. Herman Beerman and colleagues, in the February issue of the ARCHIVES, the following paragraphs should be substituted for the first paragraph on page 286.

Treatment Before Diagnosis in Venerology.—While Willcox [153] does not advocate indiscriminate treatment with penicillin before diagnosis, there are certain indications for its use, which are the following:

1. In mass-treatment campaigns against the treponemal diseases in areas of high prevalence
2. In persons exposed to unusual risk of syphilis (e. g., regular consorts of known infectious syphilitics, especially if pregnant)
3. In women whose tests have failed to show the Gonococcus but in whom gonorrhea is suspected on epidemiological grounds
4. As a prophylactic against gonorrhea after risk of infection

King [158a] is against treatment before diagnosis (abortive treatment) because it is unsound, perhaps ineffective, and often harmful. He believes that this departure from fundamental principles should be discouraged.

Books

Psychological Factors in the Care of Patients with Multiple Sclerosis for Use of Physicians. By M. R. Harrower, Ph.D., and Rosalind Herrmann, B.A. Price, Free. Pp. 32, with 5 illustrations. National Multiple Sclerosis Society, 270 Park Ave., New York, 1953.

This booklet deals with important psychological "do's" and "don't's" in caring for patients with multiple sclerosis. The physician, for instance, should help the patient discover actual satisfaction in coping with his liabilities and understand that the greater his emotional maturity, the less his disability. The "don't" most emphasized is for the physician not to allow his own disappointment or pessimism to be transferred to the patient but rather to look hopefully with the patients for remissions, which often occur and sometimes persist.

Dr. Harrower summarizes recent psychiatric and psychological studies on the personality of patients with multiple sclerosis, adding observations of her own from test results on a group of 140 patients. Tests show certain trends in disease, with reversal in remission. There seems to be impairment of intellectual and emotional functions paralleling the progression of neurological lesions. The use of psychological tests in diagnosis, counseling, and therapy is interestingly illustrated.

Adjuncts in morale building, group therapy, occupational therapy, practical devices, community resources, and rehabilitation centers are discussed. It is evident that, although we have no cure for multiple sclerosis, we have a great deal to offer in the way of management, particularly in the psychological field.

Urology: Volumes I, II, and III. Edited by Meredith Campbell, M.S., M.D., F.A.C.S.; Emeritus Profesor of Urology, New York University; with the collaboration of 51 contributing authorities. Price, $60.00 per set. Pp. 2,356 thru Vols. I, II, and III, with 1,148 illustrations thru Vols. I, II, and III. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1954.

A much-needed reference text for urology has been compiled and edited by Dr. Campbell, Emeritus Professor of Urology at New York University. He has already become widely known for his classic work, "Clinical Pediatric Urology." Urology has grown so rapidly and now encompasses such a wide field that comprehensive coverage is impossible for one author. As stated in the preface, "To achieve recognized authority for *Urology* as distinguished from mere compilations gleaned from others, outstanding collaborators were enlisted. Many of these contributions are classic monographs." Fifty-one authors collaborate with Dr. Campbell in this encyclopedic work. One receives the impression on reading through the volumes that he might be attending a conclave of essayists never before assembled for a urologic convention. Literary style, illustrative techniques, and manner of presentation vary so widely from one chapter to the next that the reader's interest is well held.

Three volumes are divided into eighteen sections. Many sections have several chapters, each chapter by a different author or co-authors. Section titles include anatomy and physiology, diagnosis, pathology of urinary obstruction, embryology and anomalies, infections and inflammations, infertility, urinary lithiasis and foreign bodies, injuries, tumors (eight chapters), neuromuscular disease, urology in the female, urology in infants and childhood, endocrinology, urologic surgery (twelve chapters), radiation treatment, medical diseases of the kidney, and the adrenal. Most chapters have exhaustive references, with cited literature as recent as 1954.

There are naturally going to be contradictory statements in any book written by numerous authors about subjects with interlocking facets. There is a typesetter's error on page 1395. But the format, physical quality, clarity of illustrations, and accuracy throughout are outstanding.

This monumental work in urology can be enthusiastically recommended to specialists in the field, for all medical libraries, and as a reference for all others seeking knowledge of the genitourinary system.

Maladies des os et des articulations. By Stanislas de Seze and Antoine Ryckewaert. Price, not given. Pp. 1,218. Ernest Flammarion, 22 rue de Vaugirard, Paris, 6e, 1954.

This is an excellent, clear, concise exposition of some of the major topics of bone and joint diseases as viewed from the standpoint of a medical rheumatologist. Many subjects, as pyogenic osteomyelitis, chronic arthritis, Paget's disease, gout, and others, are amply discussed, with special emphasis on pathology and physiology and medical treatment. Surgical treatment is merely suggested. There is, however, a tendency to oversimplify matters. I have especially enjoyed the chapter on gouty arthritis. The book as a whole has fine illustrations and can well be recommended to the profession.

Atlas of Congenital Cardiac Disease. By Maude E. Abbott, M.D. Price, $5.00. Pp. 62. American Heart Association, Inc., 44 East 23d St., New York 10, 1954.

This atlas is an exact reproduction of this classic work, which was first published in 1936, by the American Heart Association. The present issue is a limited edition of 1,500 numbered copies.

When compared to such recent works as that of Edwards and his associates, this atlas cannot be recommended as the most satisfactory current reference source. It remains, however, as a monument to the great work of the late Maude Abbott (1869-1940). Her remarkable ability bridged the gap between the previous unsystematic descriptive knowledge of congenital defects of the heart and the present understanding of the physiologic significance of these defects. Her work is a milestone in the development of the methods of precise diagnosis and dramatic surgical procedures which exist today.

This atlas is not without practical value. Its descriptions and plates are accurate. The table of statistics of congenital cardiac disease collected by analysis of 1,000 cases is still a classic. It reflects the thoroughness and critical analysis of Dr. Abbott.

The real purpose of this present reissue is to answer an intellectual and emotional appeal, and it will, therefore, be of value mainly to students, physicians, libraries, investigators, and bibliophiles who earnestly desire copies of their own.

Survey of Antimalarial Agents: Chemotherapy of Plasmodium Gallinaceum Infections; Toxicity; Correlation of Structure and Action; Public Health Monograph No. 9. By G. Robert Coatney, Ph.D.; W. Clark Cooper, M.D.; Nathan B. Eddy, M.D., and Joseph Greenberg, Ph.D. Price, $1.25. Pp. 332, with 135 tables. United States Government Printing Office, Washington 25, D. C., 1953.

This monograph is a summary of the screening data obtained in seven-day-old chicks on the toxicity and therapeutic and prophylactic effectiveness of nearly 4,000 chemical substances synthesized in 128 laboratories which collaborated during the war years in an attempt to produce effective substitutes for quinine. The data are classified according to chemical structure. In the concluding chapter the active compounds are compared with respect to therapeutic and prophylactic antimalarial action. The volume is a logical compilation of limited data and would be of great value only to investigators in the field of antimalarial chemotherapy.

Proceedings of the Annual Meetings: Council for High Blood Pressure Research, American Heart Association. By 12 collaborators. Price, $1.75. Pp. 113, with 30 illustrations. American Heart Association, 44 East 23rd Street, New York 10, 1953.

This report on the proceedings of the annual meeting of the council for high blood pressure research contains five scientific reports on atherosclerosis and one on experimental hypertension. In addition, there are six reports to the public audience concerning hypertension, arteriosclerosis and its complications, and rheumatic and congenital heart disease and heart surgery.

Under scientific reports, Gould covers cholesterol synthesis in the body as determined by studies using tagged carbon, tagged cholesterol, and tagged sodium acetate. Interchange of cholesterol between liver and plasma, extra hepatic tissues and plasma, and red cells and plasma, as well as the effect of cholesterol in the diet, were studied in dogs and rats.

In a second scientific paper Dr. Lena Lewis describes a method using a density of 1.21 for studying the electrophoretic pattern of alpha and beta lipoproteins. Normal subjects, hypertensive humans, hypertensive dogs, adrenalectomized dogs, and species notably susceptible to arteriosclerosis were studied.

In other papers are discussed the role of heparin in lipoprotein metabolism; sex and adrenal steroids in atherosclerosis; observations on local factors in the development of atherosclerosis, an important paper, and arterial injury in hypertension.

A good bit of material is covered. Included are discussions of the papers by authorities in this field.

Respiratory Diseases and Allergy: A New Method of Approach. By Josef S. Smul, M.D. Price, $2.75. Pp. 80. Medical Library Company, New York, 1953.

This little volume is divided into three parts. The first deals with "Respirallergy," a term the author employs for a wide variety of respiratory diseases including such conditions as acute recurrent bronchitis, acute recurrent suppurative rhinitis, acute recurrent suppurative sinusitis, chronic atrophic rhinitis, and bronchiectasis. He says that "after years of experimentation and observation it was found that by withholding completely milk, cream, cheese and sugar from the daily diet, a large number of patients ceased to get their respiratory trouble. Moreover, after further experimentation, it was also discovered that those who continued with the respiratory disease became well by being injected with only three substances, namely, ragweed, dust and catarrhal combined vaccine, irrespective as to how many other inhalants they proved to be allergic." If the patients are allergic to grass or tree pollen he gives them ragweed extract. Neither the classification of respiratory allergy nor this "principle" of therapy could possibly be accepted by pathologists, immunologists, allergists, or any clinicians with even an elementary knowedge of the subject.

Section 2 deals with infectious diseases of the respiratory system and is covered in a manner suitable for first year nurses. Section 3 is on neoplastic diseases of the respiratory system, and the subject matter covers one and one-half pages.

Holt Pediatrics. By L. Emmett Holt Jr., M.D., and Rustin McIntosh, M.D. Twelfth edition. Price, not given. Pp. 1,485. Appleton-Century-Crofts, Inc., 35 W. 32nd St., New York 1, 1953.

This 1953 edition (12th) of "Holt Pediatrics" has been rewritten and brought up to date with the aid of 72 collaborating authorities. In this book the high standard of previous editions has been enhanced. The authors have been conservative but have given proper evaluation to the newer methods in bringing this edition up to date. The book is authoritative, very clear, and concise and is an excellent textbook for teachers and students and a valuable reference guide for all practicing physicians.

Pheochromocytoma and the General Practitioner. By Joseph L. DeCourcy, M.D., and Cornelius B. DeCourcy, M.D. Price, not given. Pp. 165. DeCourcy Clinic, Cincinnati 2, 1953.

The title of the book might suggest a concise clear summary of a clinical problem. In this 145-page summary there is considerable repetition which seems useless. The importance, nature, incidence, clinical manifestations, diagnosis, and treatment of this disease are considered. The more recently developed diagnostic tests are given adequate consideration. There is an extensive bibliography of 361 references, most of which would not be of as much value to the general practitioner as a more extensive index. There are some editorial errors, such as the omission of the word "no," which would alter the meaning considerably. Although there is much information in this book, it hardly seems to suffice as a summary bringing order out of chaos.

Die Stuablungenerkrankungen, Vol. 2. By K. W. Jotten, W. Klosterkotter, and G. Pfefferkorn. Price, 40 DM. Pp. 424, with 273 illustrations. Dietrich Steinkopff Verlagsbuchhandlung, Einbaumstrasse 2, Frankfurt am Main-Griesheim, 1954.

This book represents 46 papers given at the second International Silicosis Meeting, at Münster, Germany, November, 1953.

It covers the entire problem from the pathological, clinical, chemical, and physical angles.

All the papers are original, and, while the clinician may be some what disappointed in the sparsity of the coverage of his field of interest, any one interested in the problem's entity, and particularly in the technical aspects of its pathogenesis, pathology, and prophylaxis, will gain a good amount of up-to-date information.

An Atlas of Pelvic Operations. By Langdon Parsons, M.D., and Howard Ulfelder, M.D. Price, $18.00. Pp. 231, with 197 plates. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1953.

This book is dedicated to and represents the teachings of Joe Vincent Meigs. It lives up to its title of "an atlas" in that there is a minimum of text and a maximum of illustrations. Each of the 197 plates contains three to seven drawings. The quality of these latter is usually good, but those illustrating vaginal operations are not as clear or understandable as those of operations via the abdominal route.

The book is very complete. In fact, many operations are included that are outside the domain of the usual gynecologist; for example, hemorrhoidectomy and combined abdomino-perineal resection of the rectum. Nevertheless, the book will be of value to the occasional operator and even to the moderately experienced general surgeon or gynecologist who proposes to do an operative procedure that is new to him.

Because of its subject matter, the book will be of little interest to the readers of this journal. The reviewer will therefore refrain from critical comments that he might make on a few of the operative techniques. He can not resist one comment, however. Only one method of removing broad ligament cysts is included. This technique also necessitates removal of the tube and ovary. This latter is practically always unnecessary and must be classed as "mutilating surgery."

Strahlendosis und Strahlenwirkung. By B. Rajewsky. Price, DM 2; $2.65. Pp. 292, with 2 illustrations. Georg Thieme, Diemershaldenstrasse 47, (14a) Stuttgart-O, 1954.

This book is based on 3,096 publications, which are cited in 109 pages of bibliography. It contains 72 pages of text and 92 pages of tables. The text is concise and gives up-to-date information about the doses of roentgen and nuclear rays, including their therapeutic uses.

The short chapters on the effect of radiation on man and animals make rewarding reading for any physician who looks for a brushing up in this field.

The clinical, hematological, and pathological results of all degrees of damage caused by nuclear and x-ray radiations are enumerated and described in sufficient detail without being repetitious.

The radiologist will quickly obtain up-to-date facts and figures from the intelligible tables, and he will find quite a repertory of the present world literature about the topic in the bibliography.

Herzkrankheiten im Säuglingsalter. By Dr. Ettore Rossi. Price, DM 65; $15.45. Pp. 373, with 198 illustrations (partly colored). Georg Thieme, Diemershaldenstrasse 47, (14a) Stuttgart-O, 1954.

This book has been fashioned in the very best Thieme tradition. The paper is excellent; the illustrations are outstanding. The title does not indicate that the author deals only with those diseases of the heart which demonstrate enlargement of the viscus.

The book is the result of work done by Dr. Rossi at the pediatric clinic of Dr. G. Fanconi, in close cooperation with Dr. M. Grob, chief of the surgical clinic of the University of Zurich.

The best way to review it is to quote to a great extent Dr. Fanconi's introduction to the book. He writes: "Up to 10 years ago the physician had to face the congenital angiocardiopathies helplessly. The best he could do was to prognosticate. This situation underwent a sudden change with the advent of heart surgery. Today, we must make the most exact diagnosis possible in order to direct the surgical procedure. It was necessary to design new methods of investigations, which furnished a more correct understanding of the anatomy of the heart. This in turn enhanced not only the development of cadiac surgery, but also the clinical cardiology, and especially the cardiology of children.

"The book begins by dealing systematically with the congenital cardiac defects in the stricter sense of the term. Newer aspects of the high interventricular septal defect, the transposition of the great vessels, tricuspid atresia, cor biatriatum triloculare, etc., are developed.

"However, the highlight of the book is to be found in the differential diagnosis of the so-called idiopathic hypertrophies of the heart. The distinction between myocarditis and myocardosis in infancy is new. The description of the glycogen-storage disease of the myocard, with its variety in symptomatology, is quite original, and so is the description of new syndromes, for example, cardiomegalia lipogenica, and polyarteritis obliterans of the coronary arteries, etc.

"For the cardiologist, the great number of well documented case histories represent a repertory of valuable observations seen from a new view point.

"The systematic analysis of the cardiopathies in infancy, explained by original diagrams, will prove to be indispensable help for all pediatricians and physicians in their daily practice."

If any book deserves to be translated into English, this is it.

The Digital Circulation. By Milton Mendlowitz, M.D. Price, $6.75. Pp. 182, with 60 illustrations and 30 tables. Grune & Stratton, 381 4th Ave., New York 16, 1954.

This book is a concise, organized presentation of all the available data on digital circulation. The preface contains the historical background from Hippocrates to the present. One chapter is devoted to each basic subject (anatomy, physiology, pharmacology, pathology) as it applies to digital circulation. Under physiology, Dr. Mendlowitz presents humoral and nervous control, as well as local factors, metabolism, hydration, anoxemia, emotion, and thermal changes, which exercise control over vascular caliber. He discusses the effect on vasomotor tone of 24 blocking drugs and 15 stimulating drugs. The chapter on pathology consists chiefly of stained microscopic sections, photomicrographs, drawings, and arteriograms.

Under the heading of methods, capillaroscopy is described and illustrated and plates of the nail-fold capillaries in health and disease are shown. Blood pressure methods are described, including the Goertner capsule, digital blood pressure cuff, double cuff technique, flushing technique, and microinjection method. Skin temperature measurement methods (thermocouples, thermopiles, resistance thermometers) are compared. The value of the Gibbon-Landis test is emphasized. Various types of plethysmographs, oscillometers, and calorimeters are described, as are radioactive sodium and fluorescin injection methods. Digital vascular resistance is defined, following Poiseuille's law.

Digital circulation studies are neatly tabulated for each of the peripheral vascular diseases, together with concise information about each condition. One chapter is devoted to clubbing. Results are presented of studies of the digital circulation in normal subjects, patients with chronic diseases, and patients with clubbing after release of sympathetic nerve tone by indirect heating. Under these conditions, in acquired symmetrical clubbing, the digital arterial pressure was found elevated and the digital flow, increased. Theories as to the etiology of clubbing and hypertrophic osteoarthropathy are discussed. The author points out a tentative conclusion that all forms of clubbing may eventually be found to be caused by local oversupply of blood brought about by various mechanisms.

Digital circulation studies in hypertensive subjects, after sympathectomy, and after coronary occlusion are presented. Current theories of the mechanism of hypertension are discussed.

The bibliography includes 636 references. The book is recommended for physicians interested in cardiovascular disease. It contains important fundamental information and original work and is very well done.

Proceedings of the Second National Cancer Conference: Volumes I and II. American Cancer Society, Inc.; National Cancer Institute of the United States Public Health Service, and the American Association for Cancer Research. American Cancer Society, Inc., 47 Beaver St., New York, 1954.

To attend and hear the papers of a National Cancer Conference is a great privilege to all interested in the problems of malignant disease. To those fortunately present, and more so to those unable to attend, the Proceedings are an amazing source of information and thoughts on cancer, both from the viewpoint of short summaries bringing general information up to date to that of current knowledge of possible etiology, behavior, and therapy and its results. A surgical resident with a recent gift of money to be used for the purchase of a book asked me which one would give the best information on cancer. I unhesitatingly recommended the two volumes I am reporting on here. They are comprehensive and written by men of longstanding investigative interest in various aspects of malignant disease. For instance, in the general sessions Dr. George Papanicolaou discusses the present status and future trends of exfoliative cytology; Dr. Alexander Haddow, of the Royal Cancer Hospital and Institute of Cancer Research, London, brings up to date recent progress in the study of chemical carcinogenesis, and Dr. Owen Wangensteen gives his views on the present status and likely future accomplishments of surgery of alimentary tract cancer. Other presentations are of equal caliber.

In Part III two round-table discussions are reported. The first one, on the significance of statistical analysis of end-results in the treatment of breast cancer sounds possibly boring, but it is alive from beginning to end. In his thought-provoking comments, Dr. James C. Lees, of England, states, among other things, that, "although treatment of cancer is based on the axiom that the earlier the treatment the better the chance of cure, it is disconcerting to find that this cannot be established numerically at all." The dissection of this idea and others by subsequent discussants is truly illuminating, and the value of frequent stock-taking on what we think we know is definitely apparent.

The second panel offers a brief but practical knowledge of steroid endocrinology in relation to breast, female genital tract, and genitourinary malignant disease. Dr. Paul Wermer's conclusions on the best curative and palliative measures for carcinoma of the breast well summarize a vast amount of experience by many groups of investigators.

Part IV deals with panel meetings on the following subjects: breast, genitourinary tract, head and neck, lymphoma-leukemia, female genital tract, gastrointestinal tract, lung, radiology, genetics, cytology, chemotherapy, virology, steroids, and isotopes.

Each one of these offers a comprehensive treatise. For example, the 35 speakers on the breast panel covered the disease from demography and the use of tissue culture in the study of exfoliative cytology, with special reference to nipple secretion, to the indications for, technique, and results of every form of treatment and their combination known today. Nineteen articles deal with therapy, and the opinions expressed by these authorities cannot fail to be of great value to every physician handling the sufferers of this commonest cancer in women today. The other panels are no less interesting and instructive, each presenting current ideas, some conflicts of opinion, and the best information available today by men most competent to give the answers.

The value of these two volumes cannot be praised too highly. They should be in the library of every physician dealing with cancer, each chapter to be read at an opportune time to absorb the important material offered and store it for future use.

Manual of Urology. By Alec W. Badenoch, M.D., Ch.M. (Aberd.). Price, not given. Pp. 555, with 343 illustrations (15 in color). Grune & Stratton, Inc., 381 4th Ave., New York 16, 1954.

"Manual of Urology," by Alec W. Badenoch, is a concise one-volume work covering the entire field of urologic practice in competent fashion. The material is presented clearly and in orderly fashion in traditional textbook style. No attempt is made to present more than "the essentials of symptomatology, pathology, investigation, diagnosis, and treatment." This book is profusely illustrated with excellent photographs and clear line drawings which serve to enhance the value of the text. The color drawings of cystoscopic views will be very helpful to the reader who has had no personal experience with the cystoscope.

The author has drawn upon his extensive experience at St. Peter's Hospital for Stone, in London, to present methods of treatment, and in many instances his preferred methods differ from those generally used throughout this country. However, all forms of therapy are generally outlined, and the bibliography includes numerous references to American as well as British literature. There are two introductory chapters on anatomy and physiology which are rather incomplete and add little if anything to the value of the book. The bulk of the text covering the various diseases of the urinary tract is clearly written and fulfills its purpose for a manual of this type. There are two final chapters on infertility and operative urology which are well done and add to the value of the book.

Medical students and others requiring a short but complete manual of urology will find this volume excellent for their purpose.

A Primer of Pulmonary Function. By Harold Guyon Trimble, M.D., and James Kieran, M.D. Price, not given. Pp. *22*, with one illustration. Printed through the cooperation of the California Tuberculosis and Health Association, 1954.

Recent advances in the diagnosis and treatment of pulmonary diseases make it imperative that adequate study of patients with pulmonary disease be carried out. It is, however, difficult for the practicing physician to find a description of the tests of pulmonary function and their application to clinical conditions. This booklet does this in an admirable manner. By reading this short monograph, one is immediately brought up to date on the current status of pulmonary function tests. It is highly recommended.

Atlas of Operative Technic, Anus, Rectum and Colon. By Harry E. Bacon, M.D., and Stuart T. Ross, M.D. Price, $13.50. Pp. 296, with 403 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1954.

This beautifully illustrated atlas of operative technique should be in the hands of every surgeon doing anal, rectal, and colon work. As stated in the foreword, by Dr. W. Wayne Babcock, the extensive experience and unusual skill of Drs. Bacon and Ross has resulted in a most descriptive monograph, wherein operations are easy to follow through a simple step-by-step text and plenty of excellent illustrations. The contents cover the general considerations of surgical anatomy, preoperative and postoperative care, anesthesia, etc. and an operative field running from malformations of the anus and rectum and hemorrhoids to pelvic exenterations. The techniques are, of course, those of the authors, and while some procedures, such as the pull-through operation for carcinoma of the rectum, are not widely accepted there is a tremendous amount of top-grade surgery available to the reader. Taking just two of the commoner subjects, one finds fistula in ano nicely depicted with a clear exposition of what complete excision of the tract means and the important point of removing overhanging skin edges to provide a wound permitting only healing from the bottom, without possible bridging or pocketing. The very useful procedure of laparotomy with colotomy and inside inspection of the colon through a sterilized sigmoidoscope is well presented. It is employed when a barium enema shows a colon polyp to be present and others are suspected. This technique should be done more frequently in our search for and removal of premalignant lesions of the bowel.

If one is already doing anal, rectal, and colon surgery, this book will provide for a comparison with the technique of established masters in that field and thus give assurance as to the soundness of various procedures or the need for change. For the beginner it is an excellent comprehensive guide to simple well-planned surgery based on sound fundamentals. For these reasons this "Atlas of Operative Technic, Anus, Rectum and Colon" should be in the library of every general surgeon or proctologist.

New and Nonofficial Remedies 1954. Price, $2.65. Pp. 609. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5; Aldine House, 10-13 Bedford St., London, W.C. 2; 2083 Guy St., Montreal, Canada, 1954.

This annual volume contains all of the drugs accepted by the Council on Pharmacy and Chemistry of the American Medical Association. Recent products are described in detail in short monographs giving indications, dosage, toxic reactions, contraindications, sources of supply, and available dosage forms. Older, well-known products are merely listed with references given to the last N.N.R. in which they were completely described. An index of distributors with a list of all their accepted products is included. This book should be on the desk of every practicing physician.

Biochemical Investigations in Diagnosis and Treatment. By John D. N. Nabarro, M.D. Price, 25 s. Pp. 299, with 5 illustrations. H. K. Lewis & Co., Ltd., 136 Gower St., London, W.C. 1, 1954.

This book contains, for its size, a remarkably complete discussion of biochemical tests and procedures available for the study of disease states. Written primarily "as a practical guide rather than a reference book," details of laboratory methods and of the background material on which the applications and interpretations of biochemical procedures are based are not included. However, adequate reference to source materials is given.

The text is divided into 14 chapters, beginning with "Disturbances of Water and Sodium Metabolism," and ending with a short chapter on "Poisoning." Procedures not generally available in hospital laboratories are discussed, as well as those usually available. Uncritical acceptance of results of test procedures is discouraged; rather the author carefully approaches evaluation in relation to the clinical history and the condition of the patient. Useful tables containing data on the normal composition of blood, urine, and feces are included, and two indices, one of investigations (tests, procedures) and one of conditions, diseases, and treatment.

The book is to be commended as a short, concise summary of a changing and rapidly expanding field.

The Year Book of Pathology and Clinical Pathology 1953-1954. Edited by William B. Wartman, M.D. Price, $6.00. Pp. 485, with 174 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1954.

The current volume contains its usual excellent review on the past year's literature. Since the subjects covered include not only pathology but also the major fields of the medical specialties, this review will be of interest to the surgeon, the internist, and any other specialist. In addition, there is a section on clinical pathology which deals with disease processes varying from blood dyscrasias to infectious diseases. The volume is attractive and well edited.

Effective Inhalation Therapy. By Edwin Rayner Levine, M.D., chairman of the committee on physiologic therapy, American College of Chest Physicians; Alvin L. Barach, M.D.; J. Winthrop Peabody, M.D., and Maurice S. Segal, M.D Price, $4.50. Pp. 157. Medical Division of National Cylinder Gas Company, 840 N. Michigan Ave., Chicago 11, 1953.

This little volume puts forth clearly the principles and methods of oxygen and other types of inhalation treatment.

The introductory chapters are concerned with respiratory anatomy and physiology and with a brief review of the mechanisms of gaseous exchange between pulmonary alveoli and blood and between blood and body tissues.

The various respiratory and cardiac diseases are taken up by chapters; the different methods by which these entities produce anoxia are explained. The technique of oxygen administration and details of the use of adjuvant measures such as bronchodilators and antibiotic aerosols are fully discussed in connection with each particular entity. Numerous simple color illustrations clarify the pathophysiology of anoxia in these diseases and show the mechanism of relief by inhalation treatment.

Dangers of oxygen therapy in emphysema and other chronic anoxic states are stressed. A description of inhalation apparatus and its use and a brief note on the relief of gaseous distention of the abdomen by the inhalation of a helium-oxygen mixture conclude this book.

There is a small glossary of terms but no index.

The book will be valuable to physicians, nurses, and technicians in improving the inhalation therapy of diseases.

Acute Pulmonary Edema. By Mark D. Altschule, M.D. Price, $3.50. Pp. 68. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1954.

This monograph is concerned with the clinical manifestations, physiologic and pathologic physiology, and treatment of acute pulmonary edema. The material constitutes a clearly written review of the literature condensed in 60 pages of text and should prove useful to student and physician.

A Manual of Tropical Medicine. By Thomas T. Mackie, M.D.; George W. Hunter III, Ph.D., and C. Brooke Worth, M.D. Second edition. Price, $12.00. Pp. 907, with 304 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1954.

It is interesting to see that Dr. Mackie has found it advisable to have numerous collaborators; the field has become so specialized that this is really unavoidable. The present volume is an outgrowth, or second edition, of that written during the last war, with special emphasis on the needs of the Armed Forces. The general spirit of the original edition has been preserved. The discussions are to the point and up-to-date. There are innumerable excellent photographs and diagrams. There are no references to the literature, but the book is already one of 900 pages and so it is probably wise not to clutter it with a bibliography. The clear and precise directions about therapy are a specially valuable feature.

The Concept of Schizophrenia. By W. F. McAuley, M.D. Price, $3.75. Pp. 145. Philosophical Library, 15 E. 40th St., New York, 1954.

"The Concept of Schizophrenia" is an easily read monograph dealing with this most important of mental illnesses. In it the author has attempted to review this disease from various angles. The beginning portion of the book deals with the historical background and traces the important developments which have lead up to the present-day understandings of

schizophrenia. The individual contributions of such important men as Kraepelin, Freud, Bleuler, Jung, Meyer, and the like are reviewed. Another section takes up the dynamic concepts of dementia praecox, and here the experimental approaches to this disorder are touched upon. There is a good discussion concerning the all-important role of heredity as well as the impingement of social and environmental conditions as they affect the total personality. The metabolic and neurophysiologic theories as they relate to schizophrenia are included. One of the concluding chapters reviews the main points in diagnosis and discusses how this disease may be differentiated from the other mental illnesses. There is a survey of the present-day methods used in treatment, along with some of the statistical results of same. This concise account should be particularly helpful for medical students desiring a good introduction to this subject, and it should prove valuable for practitioners wanting an interesting review of schizophrenia.

Metabolic Interrelations: With Special Reference to Calcium; Transactions of the Fifth Conference, Jan. 5 and 6, 1953. Edited by Edward C. Reifenstein Jr., M.D. Price, $5.00. Pp. 386. Josiah Macy Jr., Foundation, 565 Park Ave., New York 21, 1953.

This book contains an account of papers and discussion pertaining to recent experimental and clinical observations on the metabolism of calcium and of bone. It is an excellent volume for those interested in the investigative and research aspects of the subject. It would be of little value to those who are mainly concerned with treating disease involving the skeleton.

Topics considered in some detail include state of calcium in body fluids, the composition and structure of bone, the turnover of calcium in the body, and the nature and composition of bone matrix, as well as various other aspects of the subject that are too numerous to mention. Besides brief presentations of experimental results, each section contains the informal discussions by the participants in the conference on each topic presented. There are also numerous references to recent work on the various subjects discussed.

Manual of Proctology. By Emil Granet, M.D. Price, $7.50. Pp. 346, with 119 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1954.

This small book is exactly what is stated in the title—a manual—and is an excellent one. The author aims his efforts at the general practitioner and the general surgeon, and he has accomplished his mission ably. The reviewer might add that medical student and house officer, too, will find practical information in this book, especially since controversial subjects have been omitted.

It is difficult indeed for the reviewer to understand how the author has gathered so much pertinent material into a small volume.

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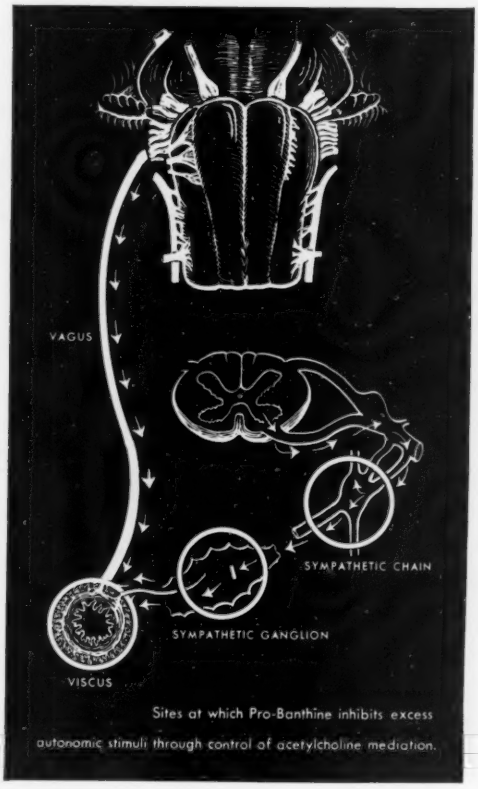

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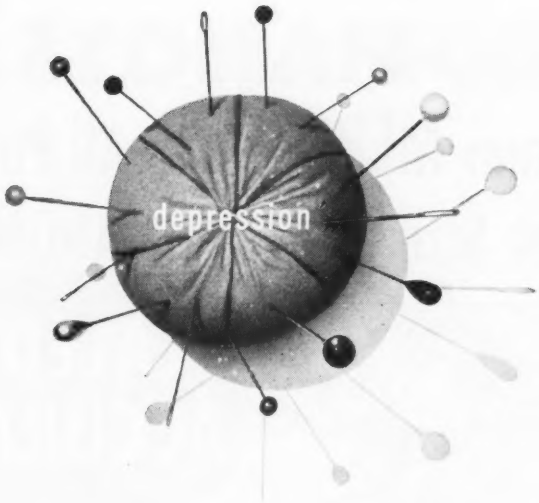

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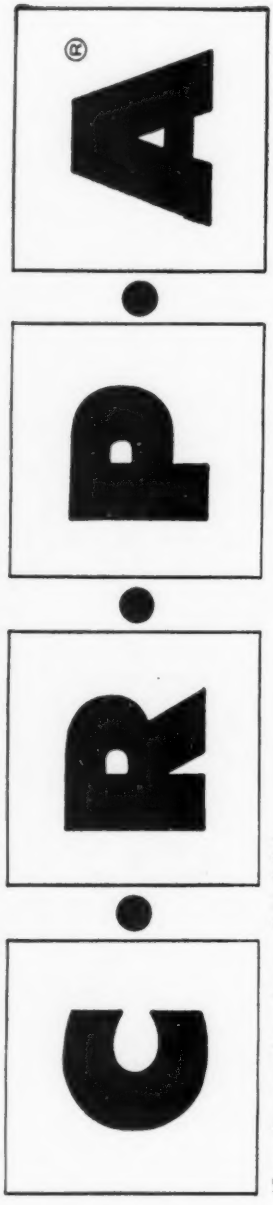

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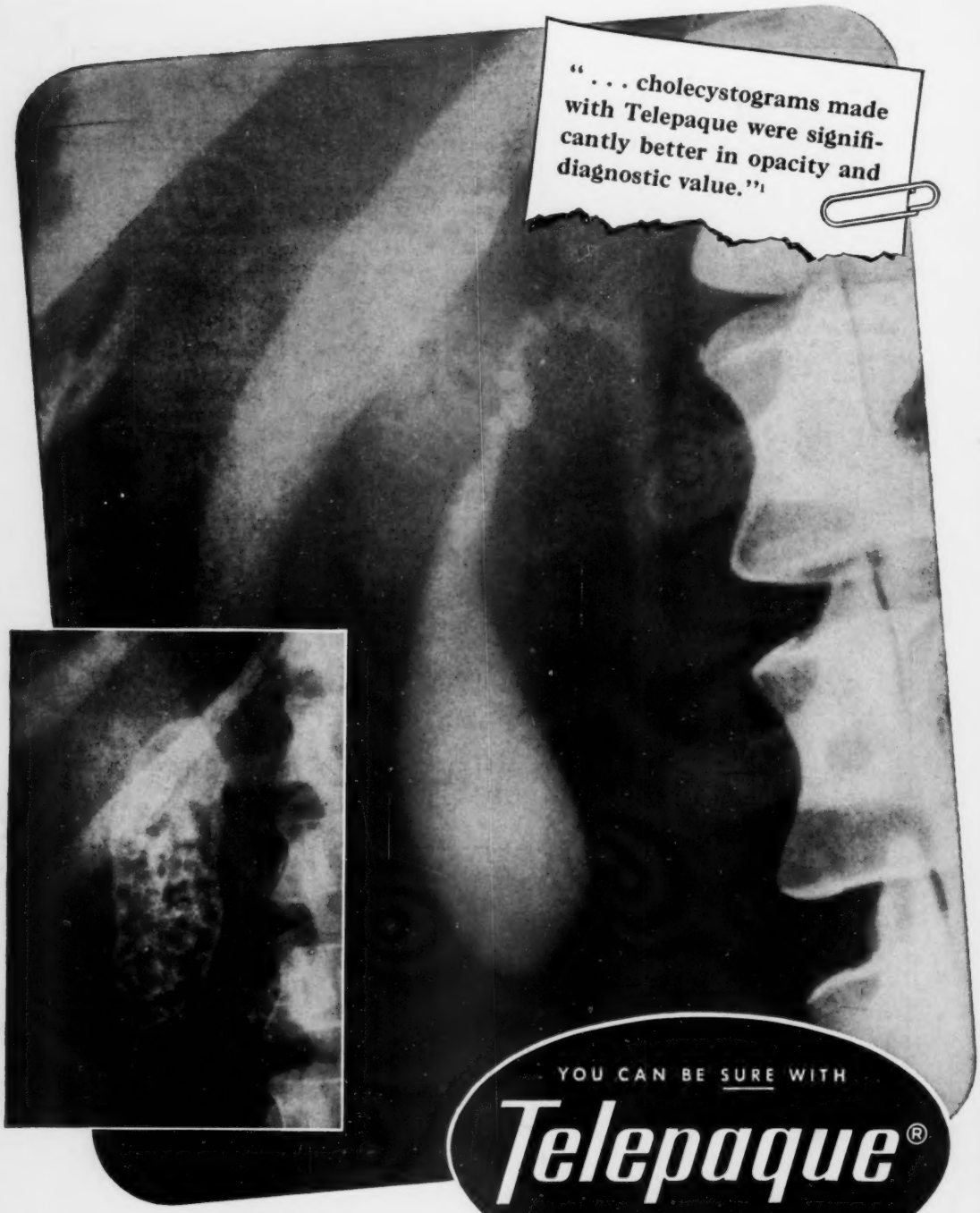

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